

DRUG EFFECTS ON MEMORY IN THE PIGEON:  
ANALYSIS USING THE BEHAVIOURAL MODEL OF SIGNAL DETECTION

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To Napoleon, Josephine, Nancy, Rebecca, Edward, Eloise,

Thomas, Samuel, Penelope, Oliver, Zoe, and Connie

- my subjects.

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Abstract

This thesis is concerned with the application of the behavioural model of signal detection to the analysis of the effects of chlorpromazine (CPZ) and haloperidol on memory in pigeons. Memory is conceptualized as behaviour under delayed stimulus control. The behavioural model of signal detection provides a way of determining a bias-free measure of discriminability and the extensions of the model to account for delayed discrimination performance allow the locus of drug effects to be determined in a quantitative manner.

In Experiment 1, pigeons worked on a delayed matching-to-sample procedure where the reinforcement rate was controlled to prevent the development of response biases. Five doses of CPZ were administered (0.5-15.0 mg/kg). There was a significant dose-dependent decrease in matching performance at doses that had no significant effect on measures of psychomotor performance. CPZ had no differential effect on matching performance as a function of the delay interval. When the performance-by-delay interval data were fit to the negative exponential and rectangular hyperbolic functions, in both cases there was a decrease in the initial discriminability but no change in the rate of decrement of discriminability. This suggested the drug was affecting the behavioural processes of discrimination, encoding, and retrieval and not memory or retention processes. This model of CPZ action was in agreement with previous research assessing the effect of CPZ on memory.

In Experiment 2, this model of CPZ action was investigated. The sample stimulus response requirement was systematically changed from FR5 to FR1. The effect on performance mimicked the effects of CPZ in Experiment 1, and suggested that both manipulations were affecting the

same behavioural processes, i.e., discrimination, encoding, and retrieval.

In Experiment 3 it was shown that the effect of CPZ could be compensated for by increasing the sample stimulus response requirement prior to drug administration. This raised the baseline level of performance and reduced the drugs' decremental effect on matching performance.

In Experiment 4, the effects of haloperidol (0.06-0.30 mg/kg) were assessed, but due to insufficient data the method of analysis derived from the behavioural model of signal detection could not be applied. It was found that the drug caused a greater decrease in matching and psychomotor performance than CPZ at doses that were approximately equivalent to the doses of CPZ administered in Experiment 1. Further the effect of haloperidol could also be characterized as a decrease in the initial discriminability but no effect on the rate of decrement in discriminability across the delay intervals.

The results are discussed in terms of methodological issues involved in the application of the behavioural model of signal detection to the analysis of drug effects. A model of the effects of CPZ and haloperidol is developed and the clinical implications are discussed. Finally the implications of the results in terms of models of pigeon memory and the analysis of behaviour in general are briefly examined.

## CHAPTER ONE

### An Introduction to the Analysis of Drug Effects on Stimulus Control

Behavioural pharmacology is that branch of biological science that uses the tools and concepts of experimental psychology and of pharmacology to explore the behavioural actions of drugs (Thompson & Schuster, 1968). The tools of experimental psychology are essentially the techniques used in the experimental analysis of behaviour and the tools of pharmacology are drugs. The discipline emerged in the late 1950's after early work by P. B. Dews demonstrated that environmental variables can modify the way in which drugs influence behaviour. Prior to that time, research on psychological effects of drugs had focused mainly on how topographically or functionally similar activities were affected by drugs (Branch, 1984). Following Dews' initial work there was a rapid increase in research as techniques derived from the experimental analysis of behaviour allowed a systematic analysis of drug effects.

Thompson and Schuster (1968) outlined the goals of behavioural pharmacology as:

- the use of behavioural observation to "screen" new chemical compounds, in order to determine their potential usefulness in medical practice,
- the use of refined behavioural techniques for the experimental analysis of the mechanisms of a drugs effect, and
- the use of drugs as a tool for the analysis of complex behaviour.

It is these last two goals that are of concern in this thesis. Within behavioural pharmacology, there are many demonstrations that subtle features of the experimental environment and the subjects' history can influence the way in which a drug affects behaviour. A drug's

behavioural effect can be modified by many variables, for example the schedule of reinforcement, the training history and the presence or absence of punishment (Branch, 1984). Of particular interest in this thesis is the relationship between a drug's effects and stimulus control.

### Stimulus Control

Behaviour can be conceptualized as the central component in a three term contingency of antecedent-behaviour-consequence. It is directly influenced or controlled by the events or stimuli that occur both before and after. The law of effect describes the qualitative and quantitative changes in behaviour which are correlated with changes in the consequences for a particular behaviour. Research on schedule control is essentially concerned with this relationship. The study of stimulus control concerns the relationship between the changes in antecedent stimuli and the subsequent changes in behaviour. Stimuli that are correlated with the occurrence of an event can come to control that event. The covariation of stimuli and responses is known as stimulus control. Stimulus control has been defined as "...the control of learned behaviour by antecedent and concurrent environmental stimuli, as a joint function of the physical specification of the stimuli and the subject's past history." (Nevin, 1973, p. 115). This definition gives a flavour of the complexity of stimulus control. It stresses that control can be exerted by stimuli prior to the behaviour as well as during the behaviour and that both the exact nature of the stimulus and the subject's past history (with that and other stimuli) interact to determine control over behaviour.

Some stimuli "automatically" control certain responses where the nature of the relationship between the stimuli and the response does not have to be learned. In these reflex responses, the response

immediately follows the stimulus. A pure eliciting stimulus is one that produces a specific reflex reaction but has no other effect. For example, stimuli that elicit protective responses in decerebrate organisms (air puff for blinking, touch for scratching) are close to being pure eliciting stimuli (Staddon, 1983).

These stimulus-response relationships can be distinguished from those which have to be learned. In the latter case the initial presence of the stimuli has no effect on the behavioural pattern. It is only after repeated pairing of the stimulus and the response (Pavlovian conditioning), or after explicit training (in operant procedures) that the behaviour may come under the control of the previously neutral stimuli.

Formal procedures have been developed for the assessment and measurement of this learned stimulus control. These differ depending on the particular process being investigated. The acquisition of stimulus control is demonstrated by the emergence of different rates or patterns of responding in the presence of different stimuli. To the extent that behaviour changes in orderly, predictable and replicable ways as antecedent and concurrent stimuli are changed, behaviour can be inferred to be under the control of the stimuli. Following acquisition of the discrimination, control may be further assessed by using generalization gradients to measure which dimension(s) or aspects of the training stimulus have acquired control over responding.

There has been considerable research on the nature of the interaction between stimuli and behaviour within the experimental analysis of behaviour. The analysis has led to an appreciation of the complex interaction that exists and of the nature of the variables that affect this interaction. What follows is a brief outline of some of the major phenomenon observed and theories developed within the

stimulus control literature. It is not intended to be an exhaustive account but rather to give an indication of the fine-grained analysis which has occurred. This account draws heavily on major reviews of the stimulus control literature (Fantino & Logan, 1979; Hearst, Besley, & Farthing, 1970; Honig & Urcuioli, 1981; Nevin, 1973; Rilling, 1977; Schwartz, 1984; Beale, Davsion, Alsop, & Elliffe, 1986)

Methods for studying stimulus control. The procedures used for studying stimulus control require the subject to respond differentially in the presence of certain stimuli. In all procedures there are a minimum of two discrete stimuli, although one may be an implicit stimulus, defined by the absence of the explicit stimulus. Stimuli are usually labelled S1...SX, or if variation in reinforcement or punishment are associated with them, S+ and S-. Discrimination training procedures can be classified in two ways. First they can be free-operant or discrete-trials procedures and secondly the stimuli can be presented either simultaneously or successively.

In free-operant procedures, the rate at which the subject responds to various stimuli or differences in the pattern or topography of responding, provides a measure of the degree of stimulus control. When the stimuli are presented simultaneously the procedure is analogous to a concurrent schedule. When the stimuli are presented successively, responses can occur at various rates or be withheld, depending on which stimulus is present. This is a multiple schedule.

Some important effects and side effects of discrimination training are observed during the acquisition of the discrimination, or during maintained steady-state discriminative performance in the concurrent or multiple schedule. These phenomenon include induction and contrast effects in multiple schedules, matching in concurrent schedules, the occurrence of "emotional" side effects with changes in

reinforcement density, and short-term within-session and between component contrast effects. One of the most intensively studied of these phenomenon is behavioural contrast. Reynolds (1961) discovered the phenomenon working with pigeons on a multiple schedule alternating in the presence of red and green lights. When one schedule was changed to extinction, the rate of responding in the presence of the S- (the light associated with extinction) decreased. There was also a substantial increase in the rate of responding under the unchanged schedule. This increase is an instance of positive behavioural contrast. Negative behavioural contrast also occurs i.e., when reinforcement is increased in the changed component, a decrease in the rate of responding in the unchanged component occurs. Several factors are important in the determination of behavioural contrast:

- the difference in the rate of reinforcement between S+ and S-,
- the species studied,
- the operant response selected for emission,
- the degree of similarity between S+ and S-, and
- the amount of temporal separation between S+ and S- (Fantino & Logan, 1979).

In discrete-trials procedures, the frequency with which the response is emitted by the subject is controlled by the experimenter. The measure of performance is response probability or proportion, rather than response rate or pattern. In a successive go-no go discrimination procedure, responding in the presence of S+ is reinforced (go trials) and responding in the presence of S- is never reinforced (no-go trials). In a two-response successive discrimination procedure, a certain response is reinforced in the presence of one stimulus and a different response is reinforced in the presence of the other stimulus. In a discrete-trials simultaneous discrimination procedure, S+ and S- are presented on the same trial and the subject



has to make the response appropriate for the S+. Response rate is controlled in these discrete-trials procedures because the response probability is 1.0 on any one trial.

Matching-to-sample procedures are more elaborate discrete-trials procedures. The basic procedure involves the presentation of a sample stimulus followed by two comparison stimuli. The subject's task is to respond to the comparison stimulus that "matches the sample". There are many variations of this basic procedure and these will be discussed in detail later.

Generalization and discrimination. The two main processes within stimulus control are generalization and discrimination. If a response that has been conditioned in the presence of a certain stimulus is emitted when other similar stimuli are presented, then the control has generalized from the training stimulus to other stimuli. If the response does not occur to the new stimuli then discrimination has occurred. Generalization therefore is a reflection of less precise stimulus control and discrimination of more precise stimulus control. The processes of generalization and discrimination are usually studied by measuring generalization gradients, which display changes in responding as stimuli are varied systematically about the training value(s).

Generalization gradients. Many important stimulus control phenomenon are observed only or principally in the generalization gradient. These include excitatory or inhibitory gradients, peak and area shift, and behavioural contrast effects on the maximum response rates observed in the generalization test.

A generalization gradient is known as a post-discrimination gradient (PDG). A PDG is formed when less responding occurs in the

presence of stimuli that are increasingly dissimilar to the training stimuli. Guttman and Kalish (1956) were the first to reliably measure the gradients of stimulus control generated by a single subject. They intermittently reinforced responding at the training stimulus while presenting the other test stimuli without reinforcement - this is known as the maintained generalization procedure. Using this procedure the subject emits enough responses to allow reliable generalization gradients to be generated.

The generalization gradient formed in a particular generalization test has certain characteristics. These are the area, height, slope, and form. The area is defined by the total gradient and as a result takes into consideration both the distribution of the responses and the range of test values. The height is the maximum level of responding along the gradient and this most often occurs at the training value. Most often it is the slope of the generalization gradient that is of most interest. A steep slope indicates strong control by the training stimulus (i.e., little generalization). A shallow slope indicates weaker control by the training stimulus (i.e., poor discrimination), or strong control by other stimuli on the dimension. The form of the generalization gradient depends on the training procedure and on the characteristics of the stimuli - their discriminability and their similarity to the training value. For example, if the stimuli on either side of S+ are not equally similar to the S+, then the form of the gradient will be asymmetrical.

The data used to generate the generalization gradient need not be the response rate, although this is the measure that is commonly used. Other variables used can be the latency, probability, amplitude or the stimulus duration. Generally the gradients obtained from each of these measures are similar. In addition, the data can be presented in various ways and these transformations can alter the shape of the

generalization gradient. Data can be presented as:

1. the absolute number of responses at each of the test stimuli,
2. as a percentage of the total responding, or
3. a percentage of responding to S+.

Gradients after training with S+ alone. Of particular interest to researchers is the way in which the generalization gradient changes following various sorts of discrimination training. In the simplest case reinforcement is given for responding at a single stimulus (S+) and responses during extinction in the presence of the S+ and other test stimuli are used to determine the generalization gradient. The variables that affect the shape of the generalization gradient obtained include:

1. the duration of training,
2. the schedule of reinforcement, and
3. the level of deprivation.

Interdimensional discrimination training. A second sort of discrimination procedure is interdimensional discrimination training, which involves using an S+ from the dimension which will be tested and a S- that cannot be located on that dimension. The negative stimulus is then presumably an "equal distance" from all stimuli on the test dimension and therefore does not interact differentially with any of them. The difficulty with this procedure is finding dimensions that are for the subjects, truly orthogonal. In general interdimensional discrimination experiments have found that training sharpens or enhances the generalization gradient around S+. In addition prior training with a stimulus on one dimension (eg. wavelength) can sharpen a single-stimulus gradient on another eg., line orientation.

Inhibitory stimulus control. Gradients obtained around stimuli correlated with positive reinforcement have been traditionally labelled excitatory. There is a decremental gradient of generalization to stimuli adjacent to the training value. The more rapid this decrement, the greater is the excitatory control exerted by the training stimulus (relative to other stimuli). Inhibitory, or incremental, gradients also exist and can be obtained from stimuli that are correlated with extinction (S-). In this case the gradient is U-shaped with the minimum at the S-. There are several ways that these inhibitory gradients can be measured:

1. Responding can be established across a range of test values.  
Extinction for responding at some central value (S-) can be introduced followed by testing over the original test values.
2. Resistance-to-reinforcement (Hearst, Besley, & Farthing, 1970),  
where inhibitory stimuli have greater resistance to reinforcement.
3. Combined cue tests, and
4. Maintained generalization tests (Blough, 1975).

Interdimensional discrimination training also allows an incremental or inhibitory gradient to be measured. By training with a S- on some dimension and a S+ that is on an orthogonal dimension, a gradient around S- can be measured in extinction. This procedure can be used to obtain gradients for both S+ and S- where opposite reinforcement contingencies exist for two groups of subjects. It is generally found that the decremental gradients are steeper than the incremental gradients.

Incremental gradients can also occur when the S- is associated with a "leaner" schedule of reinforcement than the schedule the S+ is correlated with. Terrace (1972) has argued that in order to produce an incremental gradient there needs to be reduced responding to S- relative to S+. Terrace proposed that incremental gradients were due

to the subjects non-reinforcement for responses in the presence of S-. Using an errorless discrimination procedure where the subjects never responded to S-, Terrace (1963) found no incremental gradients. However subsequent research shows that incremental gradients can arise from such "errorless" discrimination learning (Rilling, 1977).

Dimensional stimulus control. Discrimination training can also occur between two points on the same stimulus dimension. This is known as intradimensional discrimination training and involves the differential reinforcement of responding at two values on the dimension. There has been disagreement in the literature on the nature of the training required for the establishment of dimensional stimulus control. This will be briefly discussed before changes in the post-discrimination gradient following intradimensional training are noted.

For Hull and Spence, reinforcement for responding in the presence of a single stimulus from the dimension of interest was sufficient to establish dimensional stimulus control. The response strength acquired by the S+ spread to the other stimulus values in proportion to their dimensional position relative to S+. Differential training would sharpen the post-discrimination gradient but such training per se was not necessary to establish dimensional stimulus control. This absolute view is in contrast to the relational approach taken by Lashley and Wade. They proposed that dimensional stimulus control was not established without differential training at two or more points on that dimension. In the absence of differential training the effects of reinforcement in the presence of an S+ would generalize to other stimuli on the continuum, such generalization representing a failure to discriminate the distinguishing characteristics of the stimuli.

The shape of generalization gradients following non-differential training would appear to be able to resolve this issue. A flat

gradient would support the Lashley-Wade theory and sloped gradients would support the Hull-Spence theory. However both theories can account, at least in an ad hoc way, for the opposite findings. A sloped gradient is explained by Lashley-Wade adherents by the presence of unintended sources of differential reinforcement. In some cases these sources can be isolated experimentally, but in other instances the sources of the differential reinforcement are not readily apparent. The occurrence of a flat gradient is explained by the Hull-Spence supporters in terms of control by incidental stimuli.

Generally it has been concluded that differential experience with a stimulus dimension seems not to be a necessary precondition for that dimension to gain control of differential responding, which supports the Hull-Spence absolute theory of stimulus control.

Postdiscrimination gradients. Intradimensional discrimination training in which two stimuli lie on the same physical dimension produces characteristic changes in the shape of the postdiscrimination gradient. The absolutist theory of Spence makes specific predictions concerning the shape of the PDG. The theory postulates that intradimensional training would produce an excitatory gradient around the S+ and an inhibitory gradient around the S-. The net response strength at any point on the stimulus dimension is calculated by the algebraic sum of the excitatory and inhibitory gradients at that point.

Following intradimensional discrimination training, changes in the shape of the PDG are found:

1. The gradient obtained after training is sharper, although Blough (1975) has shown that the sharpness of the generalization gradient depends in part on how the responding is sampled.
2. The peak of the PDG is shifted away from the S+ in a direction

opposite to that of the S-. In addition, the area described by the generalization gradient shifts. Both peak shift and area shift are greater when the training stimuli are closer together.

The predictions from Spence's theory are in agreement with these findings but one prediction is not. Spence predicted that the height of the PDG would be less than that of a gradient obtained after single stimulus training. In fact the PDG typically has a higher peak, a manifestation in the generalization gradient of the phenomenon known as behavioural contrast. Some authors (Beale et al., 1986) have argued that since behavioural contrast is not specifically a intradimensional effect, then Spence's theory shouldn't be expected to predict it. While peak shift, behavioural contrast and gradients of not-responding tend to occur under the same conditions this does not imply that they reflect the same underlying mechanisms.

A shortcoming of Spence's theory would appear to be its incompatibility with the phenomenon of errorless discrimination learning. Since there are no non-reinforced responses in the presence of the S-, there should be no gradient of non-responding and therefore no sharp PDG. The theory can still be applied to errorless discrimination learning if the assumption is made that responses other than key-pecks, such as approaches to the key, are extinguished in the presence of the S-. Despite this problem, and the fact that the theory predicts transposition reversal when this phenomenon does not generally occur (the transposition phenomenon will not be discussed here), the theory has provided the most durable and popular account of animal discrimination learning.

Two other theories of animal discrimination learning exist. The first, a quantitative model postulated by Blough (1975), is based on the model of classical conditioning proposed by Rescorla and Wagner (1972). This model, however, has not stimulated much research. The

second approach to discrimination learning is the signal detection theory (SDT) model and this is beginning to rival the interacting-gradient model in scope and research interest (Hinson & Lockhead, 1976). The (SDT) model will be discussed in detail in Chapter Three.

Attention. Stimuli are inherently and inevitably multi-dimensional, and it is readily apparent that subjects in a discrimination procedure attend only to certain aspects or dimensions of a stimulus. This finding can be used to explain failures in stimulus control. A concept closely related to attention is that of stimulus salience. In any one situation, some stimuli gain control more rapidly than others while other stimuli may apparently fail to gain control. Those stimuli that do gain control can be said to be more "salient" for the subject. Differences in salience account for the finding that where a number of stimuli are equally correlated with reinforcement, some will acquire greater control than others (Mackintosh, 1977).

Selective stimulus control can be demonstrated using transfer tests. Reynolds (1961) showed that of two pigeons trained using a white triangle on a red background as the S+, the responding of one was controlled by the triangle and the responding of the other was controlled by the red background. In addition, selective control has been demonstrated between cues from different modalities combined into a compound stimulus. Several aspects of a compound stimulus can exert control simultaneously and pretraining with a particular stimulus can alter its salience and make it more likely that it will be attended to.

Stimulus dimensions can be classified as either criterion or competing (Honig & Urcuioli, 1981). A criterion dimension establishes control in the course of training and a competing dimension alters



this control. The temporal interaction of stimuli from these two dimensions determine the phenomenon of overshadowing, blocking and masking. Blocking may occur when the prior correlation of a competing stimulus with reinforcement prevents (blocks) the development of effective control by a criterion stimulus when the two are presented together. Overshadowing may occur when competing stimuli are presented simultaneously with criterion stimuli during training. The presence of the more intense or salient stimulus may interfere with the acquisition and/or control by the less intense or salient stimulus. In a test for overshadowing, the stimulus control maintained by one member of a compound stimulus is compared with that exerted by the same member in isolation. When competing stimuli are introduced during a generalization or transfer test, masking of the control gained by the criterion stimuli during training can occur.

These phenomenon raise the issue of where the locus of the selective action is. With blocking and overshadowing the selective process may take place at the input end of processing. However with masking the organism has already learnt the necessary discrimination but uses it selectively depending on the other stimuli present at the time. Beale et al. (1986) conclude that both masking and overshadowing yield selective effects that are not simply due to competition among stimuli at the time of testing. They are also influenced by the discriminability and the relevance of the stimuli involved.

In summary, a major reason why some stimuli fail to show control over responding is that they are either overshadowed or masked by the presence of more salient stimuli. This also accounts for why discrimination training is frequently necessary to establish control by relatively unsalient stimuli.

A wide range of factors have been found to influence the development of stimulus control. These include:

1. The degree of competition among the concurrently presented stimuli,
2. The relative discriminability of stimuli,
3. The relevance of stimuli,
4. The salience of stimuli,
5. The species of the organism,
6. Prior experience with stimuli and the nature of that experience,
7. Stimulus response-contiguity,
8. Schedule of reinforcement, and
9. Amount of training

(Beale, et al., 1986).

Before leaving this discussion two other issues related to stimulus control will be briefly mentioned.

Conditional discrimination. Complex discriminations may be established in which simple discriminations (i.e., responding in the presence of certain stimuli) can be brought under stimulus control. In these conditional discriminations, whether or not reinforcement can be obtained in the presence of a certain stimulus can depend on the presence of a "higher-order" or a superordinate stimulus. The matching-to-sample procedures, to be discussed in detail later, are an instance of conditional stimulus control. In this procedure the relation between the comparison stimuli and reinforcement is conditional on the colour of the sample stimulus. The sample stimulus can be regarded as the stimulus selecting which of the comparison stimuli will be correlated with reinforcement on any one trial.

Conceptual behaviour. This is another example of a complex discrimination where the subject generalizes within a stimulus class but is able to discriminate between classes. Discrimination training may contribute to the development of which one of the many possible

concepts become actual concepts, by singling out particular properties of stimuli as predictive of reinforcement, making them worthy of attention, and definitional of a concept. Animals can acquire the abstract concepts of same and different, where the stimulus features used to classify the stimuli are dependent on the nature of the particular stimuli that are being classified. However this seems to depend on the nature of the training procedure used. Pigeons can learn the concepts of same and different and come under the control of the degree of difference between the wavelengths on the keys. The matching-to-sample and oddity discrimination procedures generally do not show evidence of this sort of conceptual behaviour. While there is often some evidence of positive transfer from the training to test stimuli, this is far from complete (Nevin, 1973).

The acquisition of natural concepts has also been demonstrated in pigeons. A natural concept is one where there is a cluster of features that describe the members. Not all of these is shared by each member but all members have more in common with each other than they do with non-concept members. Pigeons can learn concepts such as vehicles, trees, human-made objects, and fish, and they seem to acquire these concepts more readily than concepts with clear-cut defining properties. Presumably this is because the concepts are characterized by a host of different stimulus features and the pigeon can derive information from paying attention to many of the features.

### Memory

An analysis of memory, whether in humans or in animals has generally made a distinction between short-term memory (STM) where information is held for a short time only, and long-term memory (LTM) where information is stored for later use. In models of animal memory STM is generally referred to as working memory and LTM as reference

memory (Honig, 1978). The concept of working memory can be analyzed within the framework of stimulus control, thereby providing an account of memory within the experimental analysis of behaviour. From this perspective, memory is conceptualized as the extent to which stimulus control is maintained over delays of various durations between antecedent stimuli and responses. Remembering therefore is discriminative behaviour under delayed stimulus control. Catania (1979) comments that memory within the behavioural framework is concerned with the ways in which an organisms responding can be occasioned by some event or events in the past. Imposing a delay between a stimulus and the opportunity for a response does not necessarily alter the control of the response by that stimulus.

Working memory is in fact studied using the same procedures used in the study of discrimination processes, except that a delay occurs between the presentation of the "to-be-remembered" stimulus and the occasion for the response. Within this paradigm, working memory stores the information needed to respond on a particular trial. It is limited in capacity and only holds information for a short period of time. The behavioural processes involved in working memory have been identified, and the interval between the stimulus and response determines which processes are involved.

1. No-delay: If there is no delay between the sample stimulus and the occasion for response, then only discrimination processes are involved.

2. Zero-delay: When the occasion for the response occurs immediately after the removal of the stimulus, it is assumed that in addition to discrimination processes, encoding and retrieval processes also occur. Encoding has been defined by Catania (1979) as systematic relations between stimuli to be remembered at the subsequent responses occasioned by these stimuli. Retrieval is simply what the organism

does when the response is later occasioned.

3. X-delay: When a delay of certain duration (X) occurs between the sample and the occasion for responding, the time-dependent process of retention and memory are presumed to be involved as well as discrimination, encoding, and retrieval processes (Heise & Milar, 1984).

Long-term or reference memory is a stable knowledge base containing information concerned with for example, which responses to make on a particular trial and which trial outcomes will follow. The characteristics of reference memory have been most successfully studied in animals using generalization test methods. Changes in the generalization gradients and in peak shift following intradimensional training are seen as evidence of a decrement in reference memory (Thomas, Windell, Bakke, Kreye, Kimose, & Aposhyan, 1985).

#### Drug Effects Within the Stimulus Control Paradigm

Although within the experimental analysis of behaviour there has been extensive fine-grained analysis of the processes of generalization and discrimination, and to a lesser extent of memory, this theoretical and methodological knowledge has not been extensively utilized by behavioural pharmacologists. In analyzing the interaction between drugs and stimulus control, behavioural pharmacologists have been concerned with gross issues; for example, how the degree of stimulus control is affected by drugs, how stimulus control modulates drug effects, and the effect of drugs on internal and external stimulus control. The procedures used in the analysis of drug effects and stimulus control are generally the same as those used in non-drug experiments. However, some of these procedures are more suitable than others for the analysis of drug effects.

### Free-Operant Discrimination Procedures

Operant discrimination has traditionally been defined by differential responding in the presence of a S+ and a S-. Usually one stimulus signals the availability of reinforcement on a certain schedule of reinforcement and the other signals extinction. Multiple schedules with two different component schedules, each operating in the presence of different stimuli, have also been frequently used in drug studies. Usually multiple schedules use fixed ratio and fixed interval schedules as the components. Although some interaction may exist between behaviours on the component schedules, the performance during the individual components retain most of the features of the performance of the animals working alone on that schedule (Ferster & Skinner, 1957). When performance appropriate to one or other schedule occurs only in the presence of the corresponding stimulus, there is evidence of stimulus control (Catania, 1968). When performance under these schedules breaks down with drug administration, then the drug is presumed to be affecting stimulus control processes.

Rate-dependency. There is a major limitation in using multiple schedule procedures for the analysis of drug effects. This concerns the phenomenon of rate-dependency, which occurs when a drug's effect on responding depends on the baseline rate of responding. Dews (1958a) in a study concerning the effects of metamphetamine, first suggested that a drug's effect could be predicted from the rate under non-drug conditions. The rate-dependency concept has been found to apply to a wide range of data and as a result provided the discipline of behavioural pharmacology with its first unifying principle. Branch (1984) in a review of the current status of behavioural pharmacology commented that rate-dependency became so pervasive as an explanation for drug effects that independent variables that control behaviour

were relegated to uninfluential positions. "...An analysis of drug effects in terms of behaviour mechanisms such as stimulus control, type of reinforcement, or conditioned reinforcement is unnecessary for drugs do not interact independently with such mechanisms." (Branch, 1984, p. 515). However data steadily accumulated revealing limitations in the rate-dependency concept. By the mid 1970's it was apparent that response rate was not an exclusive predictor of drug effects. For example, it was shown that the type of consequences maintaining behaviour influences the drug's effect (Barrett, 1976; McKearney, 1974). In addition, data originally seen as supporting rate-dependency were reanalyzed and satisfying alternative explanations were found (Branch & Gollub, 1974; Gonzalez & Byrd, 1977).

An exhaustive account of the rate-dependency concept is beyond the scope of this thesis (for excellent reviews see Branch, 1984; McKearney & Barrett, 1978; Robbins, 1981; Sanger & Blackman, 1976; Thompson, Dews, & McKim, 1981). For the present purposes, rate-dependency provides an alternative account of drug effects on multiple schedules. Since the non-drug response rate differs markedly between the components of a multiple FR FI schedule, drug effects may be due to differential effects on the non-drug rate of responding. Therefore it is difficult to separate the effects of drugs on discrimination processes from effects on baseline response rate. However, multiple schedule procedures have been useful in the analysis of the interaction of response rate and discriminative stimuli. Comparisons of drug effects on multiple and mixed schedules gives an indication of drug effects on internal and external stimuli. A mixed schedule is similar to a multiple schedule i.e. two or more schedules operate in alternation. In a mixed schedule however, there is no discriminative stimulus associated with each schedule.

### Stimulus Generalization Procedures

Stimulus generalization procedures have been used to assess drug effects on stimulus control. The organism is trained to discriminate certain stimuli and generalization tests under drug and non-drug conditions can be used to determine the effect of the drug on the organism's ability to discriminate. Changes in the shape of the generalization gradients after drug administration indicate if the drug had an effect on discrimination. Decreased stimulus control would be evident from a flattening of the gradient.

The effect of drugs on stimulus generalization may depend on whether the generalization is tested using a discrete-trials or a free operant generalization test. It has been found that LSD caused no change in the shape of the generalization gradient when response probability was measured in a discrete-trials procedure. However, when rate of responding was used in a free operant generalization procedure, the gradient was flattened following doses which produced decreases in high rates of responding (Dykstra & Appel, 1970).

Robbins (1981) outlines how rate-dependency can affect the results in a free operant stimulus generalization test. In a stimulus generalization test high and low rates of responding will occur. The highest rate will occur in the presence of the training stimulus and lower rates with stimuli increasingly different to the training stimuli. Therefore any drug effects may not be due to changes in sensory discriminative processes but rather to rate-dependency. A flattening of the generalization gradient would occur due to a decrease in the high rates of behaviour and an increase in the low rates. Again it becomes apparent that the procedure used in the discrimination test may influence the conclusions drawn about any drug effects on discrimination processes (Appel & Dykstra, 1977).



### Discrete-Trials Procedures

It is apparent from the preceding discussion that in order to study the effects of drugs on stimulus control, it is important to minimize the confounding effects of variations in response rate. Given this constraint, a discrete-trials procedure, where a single response is made in the presence of each stimulus, is a more appropriate method of studying discrimination than procedures in which the rate is variable (Seiden & Dykstra, 1977). Discrete-trials procedures permit exact control or description of the time of occurrence and the patterning of responses. Such procedures also make possible the experimental manipulation of the composition of the stimuli controlling behaviour (Heise, 1975). In discrete-trials procedures differential behaviour may be a right or left lever press, right or left key pecks, right or left turns in a maze, or responding in the presence of one stimulus but not in the presence of another. The measure of responding in discrete-trials procedure is a proportion - the number of stimulus occasions on which the required response occurs relative to the total number of trials - rather than a rate (Appel & Dykstra, 1977; Seiden & Dykstra, 1977). There are two main classes of discrete-trials procedures which are of interest here: discrete-trials discrimination procedures and matching-to-sample procedures.

Discrete-trials discrimination procedures. In discrete-trials discrimination procedures, the discriminative stimuli are sometimes presented simultaneously in different locations. The type of response required on each trial is the same and only its location is controlled from trial to trial by differences in the discriminative stimuli. Drug effects on overall response output would presumably affect both response locations to an equal degree, allowing for the possibility of measuring drug effects on discrimination performance somewhat

independently of effects on response rate or pattern (Ksir & Slifer, 1982), so long as responding does not cease all together.

As previously mentioned the stimuli in discrete-trials procedures can be presented one after the other in a successive procedure (eg., go-no go or two-response successive discrimination) or simultaneously where the subject has to make the appropriate response for the S+. In these discrete-trials procedures drug effects are apparent from changes in the measure of responding which is usually percent correct.

Heise and Milar (1984) note that even with discrete-trial procedures, there exists a possible confounding of drug effects on response rate with drug effects on stimulus control. This is particularly true of successive go-no go discrimination procedures where two stimuli are used, an S+ (go trial) stimulus and an S- (no go trial) stimulus. Since the control probability of responding is lower for no go trials than for go trials, selective drug effects on no-go trials responding could be considered a rate-dependent effect. This problem is avoided if two response procedures are used to examine drug effects on either the presence versus the absence of a stimulus or two values of a stimulus. For example, in both successive two-response and simultaneous discrimination, the rate of responding is controlled because the probability of response on any one trial should be 1.00.

Matching-to-sample procedures. In simple, successive, or simultaneous discriminations the discriminative stimuli have an invariant relation to reinforcement and extinction, i.e., the presence of an S+ is an occasion for reinforcement of the response and S- is an occasion for some other behaviour. The function of the discriminative stimulus is the control of a specific response. In complex types of discrimination situations, a stimulus may function as a selector of discriminations, rather than of individual responses. With conditional

discrimination (Lashley, 1938), the significance of the discriminative stimulus is not invariant, but changes in relation to the stimulus context in which it appears. The correct response cannot be made solely on the basis of a single stimulus, but must be based on the properties of two or more stimuli (Cumming & Berryman, 1965).

A discrete-trials procedure that has been used to establish conditional discriminations is matching-to-sample (MTS). A trial begins with the presentation of a stimulus (the sample stimulus) and after an appropriate response is made two or more comparison stimuli are presented. In order to obtain a reinforcer, the subject must respond to the comparison stimulus that "matches the sample" (McMillan, 1981). With pigeons colours are often used as the stimuli. On a three key response panel the centre key may come on red and following a response to that key, the side keys may come on red and green. In this case a response to the red key would earn reinforcement.

There are many variations of the MTS procedure which are determined by the temporal or conditional relationship of the sample and comparison stimuli. Sometimes the sample stimulus is present when the comparison stimuli are presented, as in the above example, and the choice response is a recognition response, as it occurs in the presence of the previously presented sample. This is known as simultaneous MTS. When the comparison stimuli are presented immediately after the sample stimulus has been terminated, the procedure is known as zero-delay MTS. In the successive MTS procedure, rather than requiring the subject to choose a correct stimulus from a set including distractors (i.e., non-matching stimuli), the subject is exposed to only one discriminative stimulus at the time of the test. Subjects are required to indicate whether the comparison stimulus is the same as the sample stimulus. Variations of the procedure exist in

which either a choice response (McPhail, 1980; Shimp & Moffit, 1977), or responding on a single key (Nelson & Wasserman, 1978; Wasserman, Nelson, & Larew, 1980) occurs in the presence of a single comparison stimulus. When an arbitrary relationship is established between the sample and comparison stimuli, the symbolic MTS procedure results. For example, a red sample stimulus may mean that pecking a comparison stimulus with black and white stripes will yield reinforcement (Kraemer & Roberts, 1984). In the oddity MTS situation the relationship between the sample and comparison stimuli is one of opposites. If a red sample stimulus is presented followed by red and green comparison stimuli, then reinforcement would be obtained for a response to the green comparison key. As with other discrete-trials procedures the response measure is the accuracy of performance, assessed using the percent correct measure. Changes in percent correct with drug administration are presumed to reflect altered stimulus control.

#### Assessment of Drug Effects on Memory

Of necessity, procedures used in the analysis of drug effects on memory have to be discrete-trials procedures as the time between the presentation of the stimuli and the occasion for the response has to be controlled. In memory experiments, stimulus control can be manipulated by varying the physical characteristics of the to-be-remembered stimulus or more commonly by varying the delay. Stimulus control is typically greatest at no-delay, less at zero delay, and then progressively declines as the x-delay duration lengthens (Heise & Milar, 1984). Procedures for evaluating memory can be divided into delayed response and delayed comparison procedures.

In the delayed response procedure, all the stimuli that specify the response are presented prior to the delay. In delayed comparison

procedures, the post-delay response is not entirely determined until after the delay, since some elements of the controlling stimuli are presented before the delay and some elements are presented after. In delayed response procedures it is possible that the subject could "bridge" the delay by means of overt mediational or coding responses during the delay. Since in delayed comparison procedures this cannot occur, it has been argued that delayed comparison procedures are more representative of everyday memory situations (Heise & Milar, 1984).

Delayed matching-to-sample. When a delay is interpolated between the sample and comparison stimuli in MTS the procedure is known as delayed matching-to-sample (DMTS). The procedure is useful as a method for the study of concept formation and short-term memory. Concept formation has been considered to be involved because operationally the pigeon must respond to the comparison stimulus "the same as" the sample stimulus, although evidence that a matching concept has developed requires the meeting of other criteria as well (Zentall & Hogan, 1978). Short-term memory has been considered to be involved in DMTS because a delay intervenes between the presentation of the sample stimulus and the comparison stimuli during which information about the sample stimulus must be retained (McMillan, 1981).

Variations in the standard DMTS procedure exist including delayed symbolic matching-to-sample and titrating delayed matching-to-sample (TDMTS). TDMTS is a procedure where the delay values that the subjects work at are not arbitrarily set by the experimenter but depend on the subjects performance. In the standard procedure (Cumming & Berryman, 1965) the delay between the sample and comparison stimuli is zero at the beginning of the session. The delay increments with correct performance and decrements with incorrect performance.

The DMTS procedure has become the preferred paradigm for the

study of animal short-term memory because it allows rigorous manipulation of stimulus parameters and precise specification of stimulus and retention interval duration (Pontecorvo, 1983). The dominant theories of animal memory over recent years have drawn heavily on the results of DMTS studies. It is therefore appropriate at this stage to review the main experimental findings and resulting theoretical accounts, since the DMTS procedure will be used in the experiments in this thesis.

#### Procedural Variables Affecting DMTS Performance

The major parameters of the DMTS procedure are the sample stimulus characteristics, the delay interval conditions and the intertrial interval (ITI). Variations in these parameters have consistent effects on matching accuracy.

A. Sample stimulus characteristics. Matching accuracy is influenced by the number of stimuli used in the sample set. As the number of items in the sample set decreases, accuracy increases (Mason & Wilson, 1974). As the presentation time of the sample stimuli increases, the matching accuracy also increases (Devine, Jones, Neville, & Sakai, 1972; Grant, 1976; Herman & Gordon, 1974; Leith & Maki, 1975; Maki & Leith, 1973; Maki & Leuin, 1977; Roberts, 1972; Roberts & Grant, 1974; Roitblat, 1980; Shimp, 1976a).

When sample stimuli are presented more than once the interstimulus (ISI) is the time elapsed between successive repetitions of the sample stimulus. Roberts and Grant (1974) found that as the length of the ISI increased performance was adversely affected and that this was true regardless of the length of the first or second presentations of the sample stimuli.

When pecks are required on the sample key greater matching accuracy results than when no pecks are required (Eckerman, Lanson, &

Cumming, 1968). It has been found for pigeons that as the fixed ratio (FR) requirement on the sample key is increased matching accuracy improves (Cohen, Looney, Brady, & Aucella, 1976; Roberts, 1972; Sacks, Kamil, & Mack, 1972; Wilkie & Spetch, 1978). In addition, performance is facilitated if pigeons must respond in different ways to the sample stimuli to produce the comparison stimuli e.g.,

1. By pecking at different spatial locations (Eckerman, 1970; Zentall, Hogan, Howard, & Moore, 1978). For example, Zentall et al., (1978) found when pigeons had to respond with five key pecks to the centre key for one sample and five key pecks to a key located above the centre key for the other, performance was better than when no pecks were required to either sample, when five key pecks were required for both or when five pecks were required for one, and nothing for the other.
2. By pecking with different response patterns (Cohen et al., 1976; Urcuioli, 1984). For example, Urcuioli (1984) showed that training pigeons to respond on a DRL schedule to one sample and a FR schedule to another greatly facilitated their performance.
3. By responding more often at one sample than another (Lyderon & Perkins, 1974; Paul, 1983). For example Lyderon and Perkins (1974) found matching performance was facilitated when a red sample stimulus required a FR8 response and a green sample stimulus required a FR16 response.

Two explanations have been proposed to account for the effects of differential sample response requirements. The first is that the samples become more distinctive and discriminable and the second is that the differential response requirements may facilitate matching by introducing an additional cue for choice - that arising from the pigeons' differential sample behaviours. A recent study by Urcuioli (1985), examined the effects of these two factors and concluded that

the facilitation in matching produced by differential sample behaviours arises from the additional cue these behaviours provide and not because they enhance discriminability.

B. Delay interval length. Across a wide variety of species it has been shown that as the delay interval between the sample and comparison stimuli increases, there is a corresponding decrease in the accuracy of the animals performance. This is the case in pigeons (Blough, 1959; Cumming & Berryman, 1965; Grant & Roberts, 1973; Roberts, 1972; Roberts & Grant, 1974; Roberts & Grant, 1976; Zentall, 1973), in rats (Roberts, 1972; Wallace, Steinhert, Scobie & Spear, 1980), monkeys (D'Amato & Cox, 1976), and a dolphin (Herman & Gordon, 1974). With pigeons a high level of performance can be maintained at 1-2 second delay and with a 10-15 second delay above chance performance can still be obtained (Zentall et al., 1978). With a group of highly overtrained birds Grant (1976) reported greater than chance performance at delays up to 60 seconds.

C. Delay interval conditions. Several studies have found that houselight illumination during the delay interval interferes with matching accuracy both in pigeons (Grant & Roberts, 1976; Maki, Moe & Bierley, 1977; Roberts & Grant, 1978a) and in primates (D'Amato, 1973; D'Amato & O'Neil, 1971; Etkin, 1972; Salmon & D'Amato, 1981). Although the level of delay interval illumination seems to be critical in obtaining the effect in primates (Salmon & D'Amato, 1981), a change in delay interval illumination relative to the baseline condition appears to be a sufficient condition for producing the effect in pigeons (Cook, 1980; Tranberg & Rilling, 1980). A study by Thompson, Van Hemel, Winston, and Pappas (1983) showed that a change in baseline conditions was not a necessary condition.

The effects of retroactive inhibition in the DMTS task have been studied by presenting stimuli during the delay interval. Jarvik,



Goldfarb, and Carley (1969) found the presence of the sample stimulus during the delay slightly facilitated matching, a novel stimulus produced a slight decrement and the incorrect stimulus produced a large decrement in performance. In a similar study with pigeons, it was found that wavelength was more disruptive than a novel shape. Jans and Catania (1980) found the operation of the feeder during the delay interval decreased matching performance relative to standard trials and on trials where pecking at the key was allowed during the delay, performance was enhanced relative to standard trials.

D. Directed forgetting. The accuracy of DMTS performance in pigeons can be influenced by the presentation of post sample cues to remember or forget (Grant, 1981b; Grant, 1984; Kendrick, Rilling, & Stonebraker, 1981; Maki & Hegvik, 1980; Maki, Olsen, & Rego, 1981; Stonebraker & Rilling, 1981; Stonebraker, Rilling, & Kendrick, 1981). Following the sample stimulus presentation one of two cues is given (e.g., a vertical or horizontal line). For one cue, (the "remember cue"), the standard procedure occurs and the comparison stimuli are presented, the other cue, (the "forget cue"), signals no comparison stimuli will be presented on that trial. After extensive training, probe trials to sample memory for the comparison stimuli are occasionally interpolated, and it is found that matching accuracy is significantly lower on forget cue probe trials than on remember cue trials.

E. Schedules controlling comparison stimulus termination. Two studies have looked at the effects of various response requirements to the comparison stimuli. In both an oddity matching (Lydersen, Perkins, & Chairez, 1977) and a DMTS procedure (Wilkie & Spetch, 1978), increasing the FR requirement on the comparison stimuli resulted in a decrease in performance accuracy.

F. Delay of reinforcement. Wilkie and Spetch (1978) found that

matching accuracy was directly related to the delay of reinforcement following correct matching, as the delay of reinforcement increased the accuracy decreased. Wilkie and Spetch conclude that the effects of FR schedules on matching accuracy may be due to the fact that high response requirements result in longer delays of reinforcement. A similar result has been found when reinforcement for correct responses in a simultaneous discrimination is delayed. Cox and D'Amato (1977) found that monkeys' choices were adversely affected when reinforcement for correct choice was delayed up to 128 seconds.

G. Reinforcement schedule. Several studies have varied the reinforcement schedule for correct responses on MTS procedures. While Ferster (1960) found accuracy increased as the size of the FR increased, this result was not replicated by Nevin, Cumming and Berryman (1963) who found that accuracy was lower on FR schedules than on continuous reinforcement schedules, but that as the FR increased accuracy increased also. When correct matches were reinforced on a FI schedule, accuracy was low in the initial portion of the interval and increased towards the end of the interval (Boren & Gollub, 1972; Clark & Sherman, 1970). On a MULT FR FI schedule, accuracy has been found to be lower during the FI than the FR component (Ferster, 1960).

H. Length of the inter-trial interval. Increasing the temporal separation of trials has been found to improve the DMTS performance of pigeons (Grant, 1975; Hogan, Edwards, & Zentall, 1981; Holt & Schafer, 1973; Maki, Moe & Bierley, 1977; Nelson & Wasserman, 1978; Roberts, 1974, 1980; Roberts & Grant, 1974; Roberts & Kraemer, 1982, 1983; Roitblat & Scopatz, 1983), monkeys (Jarrard & Moise, 1971) and dolphins (Herman, 1975). Roberts and Kraemer (1982) showed that the accuracy of delayed matching improved as the ITI length increased and the length of the delay (D) decreased. Further, the data suggested that performance remained constant at equal ITI/D ratios formed by

different lengths of ITI and D and that the percentage correct improved as a linear function of  $\log \text{ITI/D}$ . This result is similar to that found in the autoshaping procedure where the number of trials to acquisition decreases as a power function of the ITI length over the trial length (Gibbon, Baldock, Locurto, Gold, & Terrace, 1977; Perkins, Beavers, Hancock, Hemmendinger, Hemmendinger, & Ricci, 1975).

I. Inter-trial interval conditions. Two studies have shown that the trial spacing effect in DMTS by pigeons depends on the stimulus conditions during the ITI. Both successive (Santi & Grossi, 1981) and choice DMTS (Santi, 1984) performance is disrupted by long illuminated ITI's, but in general the effect occurs regardless of the ITI illumination condition during the baseline training, although there is some indication that the effect is stronger when baseline training is given with dark ITI's (Santi, 1984).

#### Models of Pigeon Memory

The extensive use of the DMTS and related procedures in experiments concerning STM have led to the development of two distinct models of pigeon working. Both models provide a good account of basic DMTS phenomenon including delay, sample duration, sample set size, and sample interference effects. Before outlining the theories some simple notation (Reynolds & Medin, 1979), describing the DMTS paradigm will be introduced.

In the basic procedure a sample stimulus (A) is presented and after a response and a delay, a choice response is offered between the sample (A) and a new stimulus (C), with a response to the sample being correct and reinforced (A+C). A common variation on the basic DMTS paradigm used to assess the effects of proactive interference is to present a sample (A), followed by a second sample (B), and after a delay interval, to give a choice between A and B with a response to B

being correct and reinforced (AB+). It has been consistently found that performance on the former control trials (A+C) is better than on the latter interference trials (AB+) (Grant & Roberts, 1973; Jarvik, Goldfarb, & Carley, 1969; Roberts & Grant, 1976).

1. Temporal discrimination hypothesis. The finding that the time between trials has a pronounced effect on matching accuracy led to the hypothesis that this may be the primary controlling variable of discriminative performance in DMTS tasks. D'Amato (1973) argues that since each stimulus appears frequently as both the sample and the incorrect test alternative, the task becomes one of determining which stimulus has appeared most recently. Thus the sample from the current trial recedes into a set of sample events organized in time and successful DMTS performance requires not simply memory retrieval but also accurate relative recency judgments. The task becomes "choose the stimulus most recently presented rather than choose the sample". So according to the temporal discrimination hypothesis, a subject need never forget a prior event. Rather performance decrement, as a function of retention interval, is due to the animal's failure to discriminate which one of a set of stimuli has been most recently presented.

The degree of difficulty of this temporal discrimination is expressed as the ratio of the time since the sample on the prior trial, divided by the time since the sample on the current trial. The discrimination becomes easier as the value of the ratio increases. Sample size effects occur because with smaller sample sets, the incorrect stimulus alternative will have served as the sample more recently. A+C control trials are predicted to be easier than AB+ interference trials, since the presentation of both test alternatives immediately prior to the delay in the the interference condition

substantially increases the difficulty of the relative recency judgment. It is predicted that increases in the ITI will facilitate matching performance by facilitating the temporal discrimination through making the sample n-to-test interval long relative to the sample n-1-to-test interval (Nelson & Wasserman, 1978).

2. Independent trace strength and competition model. This theory proposed by Roberts and Grant (1976) assumes that the presence of the sample stimulus establishes an internal representation or a memory trace. Further assumptions are that:

- a. Choice probability is directly related to memory trace strength, i.e., the stronger the trace the greater the probability of choosing the matching comparison stimulus.
- b. Strength for a stimulus is accumulated as a negatively accelerated function of time since presentation.
- c. Memory traces for different stimuli grow and decay independently.

In this model forgetting as well as remembering is strictly a function of temporal parameters (Reynolds & Medin, 1981). Accuracy is predicted to decline with increased delay, since it is assumed that trace strength decays in a negatively accelerated fashion with time.

Performance should vary with sample set size because the smaller the sample set the more likely that the incorrect alternative has recently appeared as the sample and been correct. When the incorrect stimulus serves as a sample within a trial sequence, as it does on AB+ interference trials, the strength of A will be high and A will compete strongly with B on the AB choice test (Reynolds & Medin, 1979). Long ITI's facilitate performance by allowing more time for competing stimulus traces to decay (Nelson & Wasserman, 1978).

Both theories predict very little if any proactive interference will be found on two-sample trials, if the second sample is tested

against a new stimulus (i.e., A-B-delay-B+C). This result has been found (Grant, 1975; Zentall & Hogan, 1974).

The exclusive emphasis on time linked processes in these two theories may ignore other important determinants of matching performance. For example, Medin (1976) found the magnitude of interference between trials depended on the overall similarity between trials i.e., the form, colour, and position of the stimuli. Reynolds and Medin (1981), confirmed this result and found the similarity of sample and test contexts also contributed to proactive interference.

There are several lines of evidence indicating that the assumption in the independent trace strength and competition model, that the pigeons representation of the information contained in the sample is in the form of a copy of the sample, is too simple to account for DMTS performance. First, similarity between the sample and comparison stimuli is neither sufficient nor necessary to produce matching. Following initial training with one set of three sample and comparison stimuli, Cumming and Berryman (1965) failed to find transfer to a novel pair of sample and comparison stimuli even though the novel stimuli were identical to one another. Secondly pigeons are able to perform symbolic DMTS where there is an arbitrary relationship between sample and comparison stimuli not based on physical similarity (Carter & Eckerman, 1975; Cohen, Looney, Brady, & Acuella, 1976). Pigeons matching performance seems not to be based on a single rule of the form "pick the test item most similar to the sample stimulus whose copy appears in memory" but is more likely based on a multiple rule "if sample A appears, peck test item X" (Carter & Eckerman, 1975; Carter & Werner, 1978; Cumming & Berryman, 1965).

A major weakness of both models is their conceptualization of the pigeon as a passive processor of information. There is evidence that this too may be overly simplistic. Several studies suggest that

pigeons do in fact actively process or rehearse the sample stimulus memory during the retention interval of the DMTS trial. Matching accuracy is decreased if the level of illumination is changed during the delay interval relative to baseline conditions, and this change in stimulation has been hypothesized to occupy a sufficient amount of the pigeons limited information processing capacity to interfere with the maintenance of the sample memory. Maki (1979) has demonstrated that unexpected samples more effectively control choice responding than do expected samples, suggesting that the unexpected samples receive more processing. The strongest evidence for rehearsal processes in pigeon STM come from the studies on the stimulus control of information processing in pigeons. In the directed forgetting studies rehearsal has been brought under the control of an exteroceptive stimulus. Forget cues are assumed to terminate, or at least reduce, the processes that maintain memory during the retention interval.

In view of these findings Grant (1981a) proposed a modification of the trace strength and decay model of pigeon STM, suggesting that it might be most parsimonious to incorporate an additional assumption into the model. The model could also assume that the amount of processing devoted to maintenance of the sample memory influences the level of retention in addition to factors of the initial trace strength and the rate of decay. Pontecorvo (1983) has argued that this additional assumption deprives the Grant and Roberts model of elegance and predictive value. Since the observed rate of forgetting can no longer be directly linked to the underlying rate of trace decay, the addition of a rehearsal assumption minimizes the explanatory value of the decay component. Pontecorvo suggests it may be more profitable to abandon the decay model in favour of an alternative approach where memory is seen as an active process of selection, storage, and retrieval rather than a process of passive decay or confusion.

Given that pigeons actively process information in the retention interval, attention has turned to the nature of this memorial representation and evidence suggests that this may be of a prospective rather than retrospective nature. Trace theory is retrospective because it proposes that cues to current response decisions come from residues of past stimuli (in combination with the prevailing test stimuli). Prospective accounts of pigeon memory claim current response decisions may be anticipated by the animal (Guttenberger & Wasserman, 1985; Santi & Roberts, 1985).

Several experiments have been carried out that bear directly on the prospective versus retrospective representations (Grant, 1982; Honig & Thompson, 1982; Kraemer & Roberts, 1984; Roitblat, 1980; Santi & Roberts, 1985), and while none of the experiments is definitive the data generally support a prospective position. For example, Roitblat (1980) used a symbolic DMTS procedure where colours were mapped to different line tilts. By varying the degree of similarity between hues and the angular orientation of line tilts, it was shown that most of the confusion errors made by pigeons were attributable to the similarity of the comparison stimuli and not the sample stimuli. Roitblat concluded that the pigeons were retaining information about the comparison stimuli not the sample stimuli. Grant (1982) found that the same levels of retention accuracy were obtained when successively presented samples involved either the same physical sample or physically different samples, provided they were associated with the same correct comparison stimuli. Grant concluded the data were consistent with the prospective view that a single memorial representation of the correct comparison stimulus was encoded when the sample stimuli varied but were associated with a single comparison stimulus. Further support for the prospective position comes from studies that suggest that pigeons in performing DMTS tasks actively



anticipate:

1. Response decisions (Honig & Dodd, 1983; Honig & Wasserman, 1981).
2. Trial outcomes (Edwards, Jagielo, Zentall, & Hogan, 1982; Honig, Matheson, & Dodd, 1984; Peterson, 1984; Peterson & Trapold, 1980).
3. Duration of the memory intervals (Wasserman, Grosch, & Nevin, 1982).

Grant (1981b) acknowledged that the trace strength conception of pigeon STM cannot account for the data showing that active processing occurs by rehearsal during the retention interval and that this is of a prospective instructional form rather than a retrospective nature. He proposes a new model where the presence of the to-be-remembered event activates, rather than establishes a memorial representation. Response instructions or codes held in LTM are activated in an all-or-none fashion. The probability with which a stimulus event activates its associated long term representation or code, is dependent on the relative discriminability of the stimulus event. The longer the stimulus is presented, the higher the probability that this state change will occur. Processes of maintenance rehearsal serve to increase the temporal duration of the memory activation following the offset of the stimulus originally giving rise to the activation. The probability that the activated code will return to an inactive state increases as time in the absence of the sample stimuli increases. Retention test performance in a STM procedure is therefore controlled by active memories that either remain active throughout the retention interval or become active through mechanisms of retrieval at testing. New information can be added to the memorial representation at the time of activation through the process of "tagging". Tags are proposed to represent characteristics of a to-be-remembered event that are likely to vary from occasion to occasion and therefore do not become strongly incorporated into long term memorial representations (Grant,

1981b; Roberts & Kraemer, 1983).

Roitblat (1980) and Roitblat and Scopatz (1983) have proposed a more detailed account of STM processes claiming that pigeons build up memory representations which have properties isomorphic with the correct comparison stimuli. The complex process is postulated to involve two separate components. First the animal must identify the sample stimuli that is presented on a trial. Secondly, it must query LTM to retrieve the appropriate mapping rule. Output from this analyzer drives a gradually changing memory (retention) process that codes the sample in terms of the correct response to be made. The greater the number of steps taken by this gradual memory process, the greater is the amount of information available to control choice responding. Roitblat and Scopatz (1983) propose that proactive interference acts in two ways on these processes. First there is a general interference effect controlled by the ITI duration, so that performance decreases as the length of the ITI increases. Secondly, a prechoice specific interference effect, due to the memory process only partially resetting during the ITI and always retaining a fixed amount of information about the choice most recently made.

While some authors have suggested that subjects well-trained on DMTS or related tasks use a prospective coding system exclusively (Roitblat, 1980) others argue that it is more likely that subjects use a combination of both retrospective and prospective coding. During initial acquisition, retrospective coding must occur so the subject can learn associations between the correct choice stimuli, the appropriate response patterns and the contingent outcomes (Urcuioli & Zentall, 1986).

One position concerning the dual use of the coding processes was advanced by Honig and Thompson (1982). They proposed that the time of the response decision was critical in determining if retrospective or

prospective processing occurred during the delay interval. Remembering up to the decision point, they propose, is retrospective, and related to the stimulus characteristics. Past the decision point it is prospective, and related to the response alternatives. The point of response decision appears to vary depending on the procedure used. For simple delayed discrimination the authors believe the response decision is made at the time the sample stimulus is presented. In delayed conditional discrimination and serial probe recognition tasks, the response decision is made at the time of presentation of the comparison stimuli, and the decision is made during the delay interval when dealing with memory for stimulus sequences. Honig and Thompson (1982) also suggest that it may be more useful to assess the relative amount of information required for prospective and retrospective processing to ensure correct performance. Given that animals remember anticipated outcomes and responses more readily than stimuli, after extended experience, the subject can determine the point in a trial at which the efficiency of remembering can be increased by switching from a retrospective to a prospective process, since the latter is less vulnerable to interference or the simple passage of time.

This proposal, that coding processes in DMTS and related procedures are "flexible" rather than "fixed", was taken up in a study by Urcuioli and Zentall (1986). They reasoned that pigeons trained to match highly discriminable sample stimuli (hues) to relatively less discriminable comparison stimuli (lines), may be biased toward retrospective coding. They would remember the samples instead of prospectively coding the samples in terms of their associated, but harder to differentiate, comparison stimuli. This would occur because the birds should be more likely to remember events that are less likely to be confused, because such a strategy would yield a greater frequency of reinforcement. This view was supported by the finding

that birds performing hue-line DMTS were more accurate and showed slower rates of forgetting than birds performing line-line DMTS. Since both groups matched with the same set of comparison stimuli, the finding that accuracy varied as a function of the sample dimension implicates retrospective coding at least in the hue-line group.

The most parsimonious account of pigeon working memory processes during the delay between the sample and comparison stimuli would therefore seem to be one where retrospective coding based on the sample stimuli occurred up until a response decision is made when prospective coding would occur until the response was made. The timing of the response decision depends not only on the type of task but also on the nature of the stimuli with the preferred form of coding at any one time being the form less susceptible to interference effects.

While these models account for the effects of one of the major temporal variables in the DMTS procedure, i.e. the delay between the sample and comparison stimuli, there is another temporal variable that has a major effect on performance. The trial spacing effect has generally been explained in terms of influencing the amount of interference from previous trials. A recent analysis of the effects of ITI on DMTS performance suggests that the explanation of this phenomenon in terms of a release from proactive inhibition may be inaccurate (Roberts & Kraemer, 1983). For example, it has been found, using a trial-by-trial analysis, that:

1. no interaction exists between different types of trials and the length of the ITI (Roberts, 1980; Roitblat & Scopatz, 1983),
2. spacing trials still leads to higher accuracy than massing trials even when every trial contains the same information (Roberts, 1980), and
3. variations of ITI within sessions has little effect compared with variations between sessions (Roberts & Kraemer, 1982).

There are two other hypotheses to account for the effects of trial spacing. One is the pattern perception hypothesis, and the second is an account that suggests comparison stimuli prime the representation of the sample stimuli on the next trial and that this "priming" detracts from the surprise value of the sample stimuli and is dependent on the ITI length. Neither hypothesis receives much support from experimental findings (Roberts, 1980; Roberts & Kraemer, 1982). In search of a defensible hypothesis to account for trial spacing effects, Roberts and Kraemer (1983) turned to the similarity between the effects of ITI on DMTS and autoshaping. Empirically, the effects of temporal variables on autoshaping are parallel to those of DMTS performance. DMTS accuracy, like autoshaping acquisition, increases as a direct linear function of the log ITI/delay ratio (Roberts & Kraemer, 1982; Santi, 1984; Wilkie, 1984). It is controlled more by the average ITI than by localized ITI values (Roberts & Kraemer, 1982) and free reinforcers that disrupt autoshaping also decrease DMTS accuracy (Wilkie, 1984). With the autoshaping procedure, it has been suggested that the periodic delivery of food establishes an overall or background expectancy of reinforcement (the ITI-expectancy) and this is weaker the higher the average length of the ITI, and the longer the CS is presented (T). There is a second expectancy associated with T. As the ratio of T-expectancy/ITI expectancy grows, it exceeds a threshold value and pecking occurs. As the ITI gets longer and T gets shorter, waiting time within a trial becomes short relative to the overall waiting time between reinforcers and readiness to peck increases (Gibbon & Balsam, 1981). Reinforcement expectancy is the mechanism by which scalar expectancy theory accounts for the effects of temporal variables on autoshaping.

Roberts and Kraemer (1983) suggest that with the DMTS procedure the overall temporal context in which a session takes place may exert

a further influence on performance. The variable ITI and delay length might give rise to a comparison process similar to that postulated between background and trial expectancies in autoshaping. This hypothesis is given support by the finding that trial outcome expectancies may play an important part in DMTS.

While there is some empirical evidence that is not consistent with the theory (Wilkie, 1984), Santi and Roberts (1985) assessed the role of reinforcement expectancies in the trial spacing effect in DMTS in pigeons. They reasoned that directly manipulating reinforcement expectancies during trial stimuli (using a differential outcome procedure) might alter the sensitivity of performance on these trials to spacing effects. For birds in a differential outcome condition (i.e., reinforcement with a probability of 1.0 for correct comparison responses following one sample stimulus and a probability of 0.2 for correct responses following the other sample stimulus), the ITI duration affected performance on low-probability-of-reinforcement trials only, not on both high and low probability of reinforcement trials as the theory predicts. Further, at short delays between the sample and comparison stimuli, a trial spacing effect was obtained again only for low-probability-of-reinforcement trials. For long delays, a trial-spacing effect was evident for both types of trial. These results along with the finding that the disruptive effect of ITI reinforcers is dependent on their temporal location relative to trial events are not consistent with the scalar expectancy theory.

In conclusion a fine-grained analysis of the effects of ITI, delay, and ITI reinforcers on DMTS performance when trials involve differential outcome does not consistently support scalar expectancy theory. Santi and Roberts (1985) suggest that this may be due to the fact that DMTS data reflect steady state performance and the theory has been found to be incomplete when applied to maintained autoshaping

data (Balsam & Schwartz, 1981).

Not all theories developed to account for the effects of the manipulation of various DMTS parameters use memory to account for the experimental findings. In accounting for the effects of sample duration and differential sample behaviours, the memory based theories assume that the critical factor is the amount of exposure to the sample stimulus. Spetch and Treit (1986) comment "Although a minimal amount of exposure to the sample may be essential for accurate DMTS performance, it is not necessary to assume that increases in response requirement beyond FR1, or increases in the presentation time beyond a second or two, produce their effects solely through the increase in exposure to the sample they provide" (p. 20). Spetch and Treit (1986) hypothesize that some of the effect may be due to the increased time and behaviour that have been invested in a trial by the time the choice is made. An increase in the "investment" in a trial may improve performance because errors are more costly in time or energy.

That "effort" may influence performance has been proposed by several authors in various contexts: discrimination learning (Blough, 1966), a problem learning task (Williams, 1972), a visual discrimination task (Elsmore, 1971), and DMTS (Sacks, Kamil, & Mack, 1972). Evidence for the effort or work time hypothesis comes from the work of Ferster (1960) who found that as the FR schedule requirement for matching responses increased, the accuracy increased also. In addition, it has been shown that pigeons on a FR9 schedule of reinforcement, made more errors on trials early in the FR sequence than on trials later in the FR sequence (Mintz, Mourer, & Weinberg, 1966). Both these findings are difficult to interpret within memory models of performance, but are readily accommodated by the effort hypothesis.

Spetch and Treit (1986) carried out three experiments to assess

the contribution of effort in DMTS. In the first experiment, the effects of an FR schedule on trial initiating stimuli was compared with an FR schedule on the sample stimuli. Since both FR schedules increase the total amount of effort prior to a trial they should both increase accuracy if effort contributes to DMTS performance. A memory trace interpretation would only predict an increase in accuracy by manipulating the FR requirement on the sample key. By testing various conditions where the response requirement to the initiating and sample stimulus varied, Spetch and Treit (1986) found DMTS performance was consistently enhanced by increasing the peck requirement during the sample stimuli but not by increasing the peck requirement during the initiating stimulus. A second experiment was carried out to determine if larger FR requirements meant the development of different response rates in the presence of the two sample stimuli. The authors hypothesized that the subjects might respond more rapidly during one sample than the other when 20 responses are required on both, but not when for example, only four responses are required on both. Results showed this was not the case. The ratio contingency in effect during the sample altered neither the overall rate of sample pecks or the tendency of the birds to peck at different rates during the two samples. The authors concluded therefore that effort plays little role in the effect of sample response requirements in DMTS. Rather the crucial variable appears to be the duration of exposure to the sample.

In their third experiment, Spetch and Treit (1986), addressed the issue of whether the facilitative effect is specific to situations in which matching responses are made in the absence of the sample, or whether the effect is a more general aspect of stimulus control. That is, it is possible that exposure to the sample has more to do with discriminating the critical features of the sample than remembering the sample over the delay. A simultaneous MTS procedure was used where



a facilitative effect of sample requirements could not be easily attributed to a specific effect of STM. The results showed that performance was affected by sample response requirements but not the initiating response requirements. The authors concluded that the larger sample requirements seem to improve accuracy on MTS procedures by increasing exposure to the sample, but that it is possible that this effect has little to do with STM processes per se.

### Conclusion

In conclusion, the matching-to-sample paradigm has been extensively studied and the effects of procedural variations on matching accuracy have been well documented. In addition, results from matching-to-sample experiments have been the basis of the development of models of animal memory.

The procedure is also useful in the analysis of drug effects. In particular it has been suggested that DMTS might be more sensitive to drug effects than MTS. DMTS is presumably under weaker control by the sample stimuli and control progressively weakens as the delay interval increases. Therefore drug effects might be seen at lower doses or larger effects seen at the same dose as the delay interval increases (Thompson, 1978). The MTS and DMTS procedures have been used successfully in the analysis of the effects of various drugs (Heise & Milar, 1984; Thompson, 1978).

## CHAPTER TWO

### The Effect of Chlorpromazine on Stimulus Control Procedures Assessing Discrimination and Memory Functioning.

Chlorpromazine is the drug which has often been attributed with creating a revolution in the treatment of psychoses. It was discovered by accident in the search for an improved antihistamine. Pharmacological testing found the drug had both sympathetic and parasympathetic blocking effects. Following its first successful psychiatric use in early 1952 as an antipsychotic, use of chlorpromazine spread rapidly and by late 1955, both chlorpromazine and reserpine were being widely used throughout America, from where it spread rapidly to other countries.

There are five major chemical classes of antipsychotic drugs. Chlorpromazine is a phenothiazine, haloperidol (which will be discussed later in this thesis) is a butyrophenone, and the remaining classes are thioxanthenes, dibenzoxazepines, and dihydroindolones. While the phenothiazines and thioxanthenes have a similar chemical structure, the other classes are chemically distinct and their grouping as antipsychotics depends on their ability to allay psychiatric symptoms (Winsberg & Yepes, 1978).

Antipsychotic drugs are rapidly absorbed and distributed. However, while sedation can occur within a few hours, the antipsychotic action may not be apparent for several weeks. The serum half-life is usually 24 hours or less (Winsberg & Yepes, 1978). Much of the drug (90-95%) is bound to plasma proteins, which renders it inactive. The unbound pharmacologically active portion of the drug is distributed by blood flow and because of its high lipid solubility, concentrates at high levels body in fat and brain tissue (Mason &

Granacher, 1980). This explains why excretion is slow and metabolites can be detected for weeks after cessation of chronic administration.

As the name suggests the drugs are distinguished by their ability to relieve psychotic symptoms i.e., they produce emotional quietening and indifference. In addition they are potent sedatives and sedate without producing hypnotic effects. All antipsychotics drugs share the basic property of inhibiting dopamine function in the brain. This is not the sole locus of action as no presently known antipsychotic lacks the ability to affect other neurotransmitters (Mason & Granacher, 1980). Two general conclusions are warranted concerning the drugs effect on dopamine and its metabolism. First the drugs appear to cause an initial increase in dopamine turnover, and secondly, chronic exposure to antipsychotic agents hypersensitizes receptor neurones to their transmitter. This latter finding accounts for the development of adverse treatment emergent effects such as tardive dyskinesia and parkinsonism (Winsberg & Yepes, 1978).

Use of antipsychotic drugs is widespread. They are given not only for the management of psychotic symptoms (often schizophrenia) but for a range of other disorders in various populations. In adults they are also indicated for syndromes with anxiety, aggression, motor hyperactivity, or inner restlessness as prominent features (Mason & Granacher, 1980). Antipsychotic agents for pediatric use are recommended primarily in the management of psychotic children (Winsberg & Yepes, 1978).

Chlorpromazine is one of the most common psychotropic drugs prescribed for mentally retarded people. At any one time 40-50% of institution residents can be expected to be receiving psychotropic drugs (Aman & Singh, 1983). There is evidence that this rate of medication use is decreasing and that it is lower for mentally retarded people living in community settings (Martin & Agran, 1985).

Antipsychotic drugs are used in this population for the control of hyperactivity, assaultiveness, destructiveness, self-injury, and stereotypy (Winsberg & Yepes, 1978).

Of the many side-effects of antipsychotic drugs (see Charalampous & Keepers, 1978), the one of major concern here is their effect on cognitive functioning. In adults, most studies show that patients with thought disorders show improvement with phenothiazines, whereas normal individuals show deterioration (Winsberg & Yepes, 1978). In a review of drug effects on cognitive performance, Aman (1984) concludes that of the studies examining intelligence test performance and academic achievement, a worsening of performance has been reported as frequently as an improvement. Where drug effects on attention span and short-term memory have been assessed, the results have not always been detrimental. Aman (1984) and Aman and Singh (1983) concluded that antipsychotics, especially at higher doses, may impair learning performance in mentally retarded persons.

Given that the major problem of mentally retarded people is one of learning, impairments in cognitive functioning caused by drugs are of concern. Given the practical and ethical constraints inherent in conducting drug research with humans, it is useful to develop animal models of drug action. These models can then be applied to human functioning when the major parameters of the drugs' action have been determined. Since all learning involves stimulus control, discrimination learning, and memory processes (Stoddard, 1986), an analysis of the effects of CPZ within the stimulus control paradigm adopted in behavioural pharmacology should provide useful information with which to develop a model of drug action.

#### General Behavioural Effects

One of CPZ's major behavioural effects is a reduction in

psychomotor activity. When assessed using a variety of procedures, CPZ has been found to decrease spontaneous motor activity (Dews & Morse, 1961). In small doses CPZ can cause a modest increase in the rate of interval responding, but as the dose increases, there is a progressive decrease in the response rate. Under fixed-ratio or continuous avoidance schedules, generally only monotonic decreases in responding with increasing dose are seen. CPZ has almost no ability to increase responding suppressed by punishment (Dews, 1976). There is a notable interspecies difference in the dose that causes a suppression of responding to one-half of the control rate. For rats this dose is 1-3 mg/kg, for squirrel monkeys 0.3 mg/kg and for pigeons in excess of 20 mg/kg.

The remainder of this chapter will review research into the behavioural effects of CPZ carried out within the stimulus control paradigm. Some of the procedures used in developing a model of CPZ's effect on stimulus control are not commonly used in the assessment of stimulus control but nonetheless still provide useful information about the drug's effect.

#### Escape and Avoidance Responding

Escape and avoidance procedures have not generally been used in the analysis of stimulus control, but early research investigating the effects of CPZ on escape and avoidance performance suggested that the drug was having an affect on the control exerted by the stimuli in the procedure. Among the early research into the behavioural effects of CPZ is a report by Dews (1958b). Rats were trained to climb a pole when a buzzer sounded to avoid receiving an electric shock. CPZ led to a decrease in avoidance behaviour at a dose that left the escape response intact. Dews interpreted the differential effect of CPZ as a function of the strength of the buzzer and the shock as discriminative

stimuli. The buzzer had weaker control over the pole-climbing and was more susceptible to the effects of CPZ.

There has been much further research on this phenomenon and it is now largely accepted that doses of neuroleptics that inhibit the conditioned avoidance response (CAR) do not generally block the escape response (ER). This is true whether the procedure used is a discrete-trials or continuous avoidance procedure. In a discrete-trials avoidance procedure a warning stimulus is followed by an unconditioned stimulus if an avoidance response does not occur within a certain time. The shock can be terminated by the escape response. In the continuous avoidance procedure, shocks are set to occur regularly in the absence of responding (the shock-shock, S-S, interval). However, each response can delay the onset of the shock for a specified period of time (the response-shock, R-S, interval). Both avoidance and escape responses are possible: avoidance responses reset the R-S interval and the escape responses will terminate the shock.

The results obtained by Verhave, Owen and Robbins (1958) are typical of those found when these procedures are used to evaluate the effects of CPZ. Rats were trained to turn a wheel in order to avoid or escape shock. A buzzer sounded for seven seconds prior to the shock and remained on until the shock was presented or a response had occurred. CPZ, (4.0 mg/kg), decreased avoidance responding to 50% of the control level of responding while escape responding remained at 95-100% of the control level. Smaller doses produced a similar effect but avoidance responding was reduced less, i.e., 2.5 mg/kg decreased avoidance responding to 40% of the control level and 1.6 mg/kg decreased it to 60% of the control level with, in both cases, negligible loss of escape responding. Similar results are obtained from experiments using a variety of methodological approaches and subjects, including humans (Cook, 1964; Fishman, Smith, & Schuster,

1976).

The role of discriminative stimuli. While a portion of the neuroleptic-induced anti-avoidance effect can be explained by either response, reinforcer, or organismic variables and their interactions (Bignami, 1978), a wide range of stimulus factors have been shown to influence the antiavoidance action of neuroleptics. These include:

- a. attenuation of CPZ effects with increased shock intensity (Irwin, 1960; King, 1970; Nigro, 1967).
- b. attenuation of CPZ effects with more intense signals or with easily detectable cues (Chipman, 1966; Irwin, 1960; Polindora & Urbanek, 1964; Posluns, 1962).
- c. Greater drug sensitivity in the presence of short relative to long CS-US intervals, although there are some differences in results probably due to methodological differences between experiments (Lipper & Kornetsky, 1971; Low, Eliasson, & Kornetsky, 1966; Posluns, 1962).
- d. Lower drug sensitivity in discrete-trial than in continuous avoidance schedules (Chalmers & Erickson, 1964; Dobrin & Rhyne, 1969; Heise & Boff, 1962; Herman, Malick, & Kubena, 1979).

In summary, any increase in the complexity of the discrete-trials conditioned-avoidance procedure renders the response more sensitive to suppression effects by CPZ.

Two other studies may serve to illustrate the influence stimulus factors have in the differential effect of CPZ in avoidance procedures. A study by Cook, Davison, Davis, & Kelleher (1960), showed that in dogs conditioned to avoid a shock following the injection of epinephrine or the presentation of a tone, CPZ (0.5-2.0 mg/kg), suppressed the CAR to epinephrine at lower doses than those required to suppress the CAR to the tone. The authors concluded there was a continuum of suppression effects produced by CPZ: epinephrine > tone > shock. A similar finding was reported by Maffi (1959) in an experiment

using pole-climbing in rats. Maffi evaluated the relative strengths of an unconditioned response (to the shock), a primary conditioned response (to the tone), and a secondary conditioned response (the response that occurs when the rat is put in the apparatus prior to the CS). The ED50 for CPZ (the dose causing a 50% loss of the climbing response), was 1.75 mg/kg prior to the tone, 11.6 mg/kg during the tone, and 33mg/kg when the shock was present, indicating the differential strengths of the stimuli controlling the responding.

These findings concerning the importance of discriminative stimuli in the effects of CPZ on conditioned avoidance responding led to speculation that neuroleptics may not abolish avoidance responding per se, but rather attenuate arousal and/or stimulus sensitivity (Irwin, 1960, 1963; Janku, 1964). Such a model was proposed by Dews and Morse (1961). They speculated that the differential effects of CPZ were not based on a dichotomous distinction between avoidance and escape behaviour, but that its effect was to attenuate the power of stimuli to occasion responding. Therefore the effects of CPZ would be seen first (in the sense of at the lowest dose) on the response of least efficacy for escape/avoidance.

This accounts for many of the results obtained using discrete-trials and continuous avoidance procedures. For example, in discrete-trials avoidance procedures the CS (warning stimulus) is weaker than the US (shock) therefore the avoidance response is affected at lower doses than the escape response. Discrete-trials avoidance procedures are less sensitive to the effects of CPZ than continuous avoidance procedures because of the presence of an external stimulus (tone, light, or buzzer) which signals the onset of the shock. In continuous avoidance procedures the animal has to rely on "internal" stimuli to control the timing of the responses. These "internal" or temporal stimuli (Anger, 1963), are weaker than the external cues and therefore



are more susceptible to the effects of CPZ. Such a model also easily explains the results of Cook et al. (1960) and Maffi (1959) where the weaker stimuli either internal (epinephrine) or less highly associated with the US (the environment of the apparatus) were influenced by lower doses of CPZ. It also accounts easily for the effects of increased shock intensity and more intense signals or cues.

Other models have been proposed to explain the effects of neuroleptics on avoidance paradigms. However, neither the model based on the drug's ability to attenuate fear motivated behaviour while leaving pain motivated behaviour intact, or the model postulating an explanation at the motor system level, provide adequate accounts of CPZ action (Beninger, Mason, Phillips, & Fibiger, 1980 a,b; Bignami, 1978; Grilly, Johnson, Minardo Jacoby, & La Riccia, 1984).

An alternative model has suggested that the important variable controlling drug effects on avoidance responding is the degree of response strength (Barry & Buckley, 1966; Bignami, 1978). A recent account of this model by Grilly et al., (1984) proposed that response strength is dependent on many factors including the intensity of the CS and the US, the type of response required, the degree of motivation, the amount of acquisition training and the response biases. In an evaluation of this model, response strength was varied by changing the shock intensity. When the avoidance and escape responses were of equal strength, CPZ impaired the escape and avoidance responses to the same extent (Grilly et al., 1984). Response strength in this experiment was manipulated by altering the shock intensity. The influence of the shock intensity as a stimulus factor is well known and unless the other components of response strength can be shown to have a similar effect on avoidance and escape responding, it may be more parsimonious to account for the effects of CPZ in terms of stimulus control rather than response strength.

### Stimulus Significance

The concept of stimulus significance has been used by several authors in their explanation of the effects of CPZ. While some have used procedures common in the analysis of stimulus control, others have used novel procedures. The term was first introduced by Key (1961) to account for the effects of CPZ in cats trained in a barrier crossing escape-avoidance task. Key concluded that with CPZ, "the amount of generalization is less and stimuli lose the significance attached to them by the animal resulting in the indifference and lack of responsiveness to sensory stimuli characteristic of the central action of this drug" (Key 1961, p. 362).

F. N. Johnson has written extensively using the term stimulus significance to account for the effects of both chlorpromazine and lithium (Johnson, 1972). Use of the term "significance" carries connotations of some degree of analysis of stimulus input where sensory information is evaluated in terms of meaningfulness given the organism's past experience or innate requirements. The implication of some form of stimulus processing is much stronger than when the term control is used. Johnson argues that a stimulus significance model of the effects of CPZ would account for both the attenuation by the drug of behaviour established under aversive control and its subsequent extinction and effects using multiple schedules. He also argues that it accounts for the general finding that CPZ reduces inter-subject hostility (for an example see Norton & DeBeer, 1965). Other authors comment that this concept could be used to account for why CPZ and related drugs protect against the enhanced lethality of amphetamine to grouped mice (Dews & Morse, 1961). Dews and Morse comment that such results may be due to the ability of CPZ and related drugs to reduce the efficiency of stimuli controlling and directing behaviour.

Johnson (1971 a,b) made an indirect test of his stimulus significance hypothesis when he increased the stimulus significance prior to the administration of the drug. Reasoning that if CPZ decreased stimulus significance, then pretreatment training should offset this effect. In two studies mice were trained to avoid the black compartment in an apparatus consisting of two equally-sized compartments, one black and the other white. CPZ (0.075 mg/kg) impaired the acquisition of the passive avoidance learning (Johnson, 1971a), and in a dose of 2.0 mg/kg impaired the expression of the learning (Johnson, 1971b). In both these studies the drug effects could be offset by increasing the stimulus significance by prior training in a T-maze involving a black-white discrimination.

More recently Johnson (1983 a,b,c) proposed a stimulus analysis model of mood disorders and outlined an experimental technique to assess whether a particular drug is a suppressor of stimulus processing efficiency. The experimental paradigm used by Johnson was passive exploration in rats. When using exploration activity to measure drug effects it is often difficult to distinguish between a drug-induced reduction in exploration caused by an effect upon sensory analysis and a reduction resulting simply from suppression of motor activity (Hughes, 1982). Johnson reasoned however that when the index of exploration was the time for which an animal remained at rest in the presence of novel stimulation, then a drug induced reduction in responsiveness to environmental cues (stimulus significance) would lead to an increase in locomotor activity while an effect on motor activity would be reflected in reduced locomotion. Johnson (1983b) derived a behaviour change index using this logic, and showed how changes in it could be taken to reflect characteristics of stimulus analysis and motor activity. Using this procedure the effects of a single dose (1.0 mg/kg) of CPZ were analyzed. It was found that the

CPZ produced a distinct impairment of stimulus processing efficiency but had relatively little effect upon motor activity.

Several authors have examined the effects of CPZ within a model of stimulus efficacy. Clody and Carlton (1980) proposed that stimuli more proximate to reinforcement, or that are correlated with greater degrees of reinforcement, may both be relatively more efficacious in controlling behaviour than stimuli less proximate to reinforcement. Migler (1975) reported data supporting Clody and Carlton's account of CPZ action using a conditioned approach situation, an analogue of conditioned avoidance, where food reinforcement was used instead of shock avoidance or escape. Each trial consisted of illumination of a response disc with yellow light for a maximum of 15 seconds (with a tone present for the first second of the light). A response to the disc during its illumination resulted in the immediate delivery of a reinforcer. If a response was not made within 15 seconds a "free" reinforcer was delivered. Using squirrel monkeys, CPZ (1-6 mg/kg) reduced the frequency of responses to the approach stimulus (the yellow light) while preserving short latency responses to the free food pellet. Such results would be expected on the basis of the variations in stimulus efficacy imposed by the differential proximity of the two stimuli to reinforcement.

Extending Migler's study, Clody and Carlton (1980), using rats as subjects, looked at the effects of CPZ in a procedure where they varied stimulus efficacy in terms of both the proximity to reinforcement and the magnitude of reinforcement. CPZ (1-4 mg/kg) decreased all response indices, but the responding controlled by more efficacious stimuli (i.e. the presence of food versus a tone or a light) and greater reinforcement magnitude (three pellets versus one) was consistently less affected. In both the conditioned approach and conditioned avoidance procedures responding to the warning signal is

less proximate to primary reinforcement than is responding to the shock or the food and Clody and Carlton conclude that in both cases the effects of CPZ on stimulus efficacy can account for the results obtained.

#### Acquisition and Extinction of Stimulus Control

CPZ has been found to affect the acquisition of various types of avoidance responses where responding is under weaker stimulus control than when the task has been fully acquired. In general animals treated with CPZ will increase the number of trials needed to attain the acquisition criterion (for example, Appel, Freedman, & Filby, 1967; Bravo & Appel, 1967; Doty & Doty, 1963; Johnson, 1971a; Sansone, Renzi, & Amposta, 1972). The magnitude of the drug effects on acquisition may depend partly on the test situation. Doty and Doty (1963) found that CPZ caused a slight decrement in the acquisition of a runway avoidance response, and when the test was made more difficult by requiring the animal to select the lighted one of two adjacent compartments, the CPZ produced a much greater decrement.

CPZ administered before testing a learned avoidance response results in an increase in the rate of extinction of that response (for example, Miller, Murphy, & Mirsky, 1957a, 1957b; Key, 1961; Johnson, 1971a). Miller et al., (1957a) found a more rapid extinction of avoidance responses following CPZ, which was independent of sedational effects or motor impairment. In a second study, Miller et al., (1957b) reported more rapid extinction of a shuttlebox avoidance response in rats under CPZ than under saline, and that extinction persisted when the CPZ was discontinued. In this situation, the effect of CPZ can again be explained by it causing an attenuation of the control of the stimuli which resulted in more rapid extinction of the conditioned response.

More recently another procedure has been used to assess the effects of drugs on stimulus control. Modifying a procedure similar to one developed by Boren (1963), Thompson (1973) used repeated acquisition of behavioural chains by pigeons to assess drug effects. Each subject acted as its own control thereby minimizing the influence of inter-subject variability. Subjects were presented with three response keys, all of which were illuminated at the same time by one of four colours. The pigeons task was to learn a four-response chain by pecking the correct key in the presence of each colour. For example, a sequence may be when the keys are yellow - peck the left key, when they're green - peck the right key, when they're red - peck the centre key and when they're white - peck the right key. After pecking the correct sequence the pigeon was reinforced. An incorrect response resulted in a 5 second timeout. The sequence of correct key positions was changed from session-to-session but the order of the associated colours was always the same. After 40-60 training sessions the subjects reached a stable level of performance as characterized by the total errors per session.

CPZ (0.5-8.0 mg/kg) did not affect the overall accuracy across the dose range tested, although there was a slight error increasing effect at the largest doses during the first part of the session, and increased pausing at the larger doses. This lack of significant effects was probably due to the relatively low dose of CPZ used and the author comments that had higher doses of CPZ been tested the overall accuracy would have been impaired.

In a subsequent experiment (Thompson, 1974) performance was compared in a learning situation, where the four response chains changed from session-to-session, and a performance condition where the four response chain was the same from session-to-session. In contrast to the learning condition, the error rate was relatively constant and

near zero in the performance condition. Chronic administration of CPZ had little disruptive effect in the performance condition, in contrast with the error-increasing effect under the learning condition.

Thompson concluded that the learning condition was more sensitive than the performance condition since it was a more "complex" task and that the two conditions represented strong versus weak stimulus control (Thompson, 1978; Thompson & Moerscheacher, 1978, 1979).

#### Free-Operant Discrimination Procedures

Various multiple schedules have been used in the determination of the effects of CPZ. Several authors have reported the effects of CPZ on performance in S+/S- multiple schedules. Dews (1963) reported a study in which a multiple fixed ratio 25 extinction schedule, MULT FR25 EXT, was used to establish a S+/S-discrimination in pigeons. A 27 mg/kg dose of CPZ disrupted the S+ responding but it did not lead to any S- responding, which Dews interpreted as meaning that there was no interference with "discriminatory behaviour". This finding was replicated using a different procedure by Wiltz, Boren, Moerschbaeher, Creed and Schrot (1974), who used a multiple variable interval one minute extinction schedule, MULT VI1min EXT, with pigeons. Increasing doses of CPZ (10-30 mg/kg) produced progressive decreases in the rate of S+ responding but did not lead to any S- responding.

Terrace (1963) compared the effects of CPZ administered to two groups of subjects. One group learned the S+/S- discrimination with errors and in the other group errorless learning was established using a fading procedure. CPZ (1, 3, 10, and 17 mg/kg) caused no errors in the subjects taught using the errorless discrimination procedure, whereas there was an increase in responses to the S- by the subjects taught the discrimination with errors. Terrace explained these results

by hypothesizing that when the discrimination was learned with errors, CPZ reduced the aversiveness of the S- and facilitated S- responding. However, it may be more parsimonious to account for the findings simply in terms of stimulus control. Discrimination performance learnt with no errors is likely to have been under much stronger stimulus control than that formed with errors, and this would account for the differential effect of CPZ.

A more commonly used multiple schedule is one where two different component schedules of reinforcement operate sequentially, each in the presence of a different stimulus (Thompson, 1978). These will be denoted S1/S2. When multiple fixed ratio-fixed interval schedules, MULT FI FR, are used CPZ has been found to have characteristic effects by many researchers (Barrett, 1983; Bignami and Ghatti, 1969; Dews, 1958c; Leander, 1975; Leander and McMillan, 1974; McMillan, 1971; Wenger, 1979).

Generally there is a decrease in the rate of responding in both the FR and FI components of the schedule, but performance in the FR component is more resistant to the suppressive effects of CPZ. For example, Leander (1975) found that in pigeons working on a MULT FR30 FI5min schedule, a 100mg/kg dose of CPZ decreased the FR rate to 70% of the control rate and the FI rate to 48% of the control rate, with the FI rates being decreased relatively more than the FR rates throughout the dose response curve.

Another indication of weakened stimulus control in MULT FR FI schedules is the intrusion of FR-like responding during the FI component. Waller (1961) used a MULT FR50 FI3min EXT schedule in a dog and found CPZ (12-24 mg/kg) produced short bursts of responding in the FI component. These bursts disappeared when the FR component was removed and Waller concluded "the responding observed after the high doses with the FR component intact is probably a function of induction



i.e. loss of stimulus control" (Waller, 1964, p. 355).

These results can be explained in terms of the different degrees of stimulus control over responding on the two schedules. In the S+/S- multiple schedule the discrimination is relatively easy and therefore responding is under strong stimulus control and is resistant to the effects of CPZ. Although each component of the S1/S2 multiple schedule is signalled by an external stimulus, the FR schedule is under stronger stimulus control because each response acts as a conditioned reinforcer (as it directly contributes to the attainment of reinforcement). In the FI component, the animals performance is under the additional control of internal stimuli indicating the passage of time and this more weakly controlled behaviour is more susceptible to disruption by CPZ. This analysis of the effect of CPZ on MULT FR FI performance closely resembles that of the drugs effect on conditioned avoidance responding.

A study by Leander and McMillan (1974) comparing the effects of CPZ on a mixed and multiple FR30 FI10min schedule, also supports this interpretation of the effect of CPZ. During the multiple schedule two different stimuli were associated with the two different schedule components, while in the mixed schedule one stimulus was present during both schedule components. The presence of the external stimulus in the FR component of the multiple schedule made responding resistant to the effects of CPZ compared to the FR component of the mixed schedule, where the response rate decreased. Responding in the FR component of both schedules was more powerfully controlled by the schedule-correlated stimuli than responding under the FI component, and was therefore more resistant to the suppressive effects of CPZ.

Rate-dependency. CPZ and a variety of other phenothiazines produce rate-dependent effects on FI schedules (Dews, 1962; Fry,

Kelleher, & Cook, 1960; Leander, 1975; Leander, 1981; Leander & McMillan, 1974; Wenger, 1979). These drugs increase very low rates of responding that occur early in the FI and decrease high rates later in the interval despite the fact that they generally decrease overall response rates (Seiden & Dykstra, 1977). The rate-dependent effects of CPZ have also been observed in a second order schedule (Marr, 1970).

There are several ways of quantifying FI response patterns (although none is without criticism). One is the quarter life, which is the proportion of the interval required for the first 25% of responses to occur. CPZ has been reported to decrease the quarter life at doses which do not decrease the overall FI rate of responding in pigeons (Leander, 1975), and in rats (Clark, 1969). Another measure of response distribution is the index of curvature (Canon & Lippa, 1977; Fry et al., 1960; Laties & Weiss, 1966). A large positive value in the index of curvature indicates responding occurs primarily in the terminal portions of the interval, a value of zero indicates an equal rate of responding throughout the interval and a negative value indicates responding was mainly at the start of the interval. Canon and Lippa (1977), using a FI2min schedule with rats, report that administration of CPZ produced a dose-dependent decrease in the index of curvature. In the 2.5 mg/kg condition the index of curvature was 0.57, for 5.0 mg/kg it was 0.41 and for 0.24 the index of curvature had fallen to 0.24, indicating that with increasing CPZ dosage the distribution of the responses in the FI was changing.

#### Modulation of multiple schedule performance by external stimuli.

The phenomenon of rate-dependency means it is difficult to use multiple schedules in the study of drug effects on stimulus control unless the rate-dependent effects of these drugs can be ruled out as an alternative explanation (Thompson, 1978). However multiple

schedules have been successfully used to show how the effects of drugs can be modified by the intensity and mode of presentation of environmental stimuli associated with the schedule under which the behaviour is maintained (Seiden & Dykstra, 1977).

Laties and Weiss (1966) used two different FI schedules to determine whether behaviour controlled by internal stimuli was more sensitive to modification by drugs than behaviour controlled by external stimuli. One schedule was a regular FI5min schedule where the only discriminative stimuli were those arising from the pigeons own body or its own behaviour. The other FI5min schedule had a "clock" - a sequence of five symbols which appeared during successive minutes of the interval. Control responding, as measured by the index of curvature, showed a mean of 0.74 for the "clock" condition and 0.34 for the "no-clock" condition. Across a range of CPZ doses (1.5-12.0 mg/kg) the index of curvature decreased under both schedules with the decrease being relatively greater in the "no-clock" condition. In both cases this was due to increased responding in the first four minutes of the interval. This result was in sharp contrast to the other drugs tested (amphetamine, scopolamine and pentobarbital) where the presence of the clock kept the performance comparable to baseline levels. Laties and Weiss (1966) speculate on why the source of the stimulus (i.e. internal or external) should make a difference, commenting that the location of the stimulus may be important only because of a correlation with another variable that is itself related to drug sensitivity.

A second study by Laties (1972) minimized the influence of baseline rate by using a fixed consecutive number schedule (FCN). Pigeons had to make eight or more responses on a white key before responding on a green key would be reinforced (FCN 8). In the second condition, the eighth consecutive response on the white key changed

its colour to red which signalled the availability of reinforcement on the green key (FCN 8-S). Control data showed that where the discriminative stimulus was present the mean run length was closer to eight and there was a higher percentage of reinforced runs. There was no difference in overall response rate or rate during the runs between the schedules. CPZ (doses 1.0-81.0 mg/kg) caused a decrease in both measures of response rate and caused the mean run length to decrease progressively on the FCN 8 schedule, while not changing much on the FCN 8-S schedule. On the measure that best reflected control by the added discriminative stimulus, the percentage of reinforced runs, CPZ caused a decrease under both schedules, but more so for the FCN 8 schedule. For example, the 81.0 mg/kg dose reduced the percentage of reinforced runs to 41% for FCN 8-S and to 20% for FCN 8. These results are in agreement with those obtained by Laties and Weiss (1966). In both studies CPZ modified behaviour even with the addition of an external stimulus. The latter study showing that with the influence of response rate minimized behaviour under external stimulus control, while still being disrupted by CPZ, was less disrupted than behaviour under internal control.

While some authors argue that phenothiazines do not disrupt stimulus control at all and that the effect of these drugs can be explained entirely by the rate-dependency concept (Leander, 1981), others see drug effects as an interaction between schedule and stimulus effects (Laties & Weiss, 1966). The suggestion has been made that the rate-dependency phenomenon could arise from impaired stimulus control. Robbins (1981) argued that if two different rates and patterns of responding are maintained in the presence of two randomly occurring components in a multiple schedule, and if they are exposed to a drug that impairs the sensory processing of wavelength, then the impairment may be expressed as similarities in the rate of responding.

This would cause an increase in the initial portion of the FI and a decrease in the terminal portion i.e. a result usually explained in terms of rate-dependency.

However to provide exact tests of drug-induced alterations in covert processes, inferred by changes in rate, it is necessary to use tests of discriminative sensitivity which are largely independent of the rate of responding. Since the rate and pattern of responding are altered by drug administration, the drug effects on discriminative control have to be separated from the effects on the measure of stimulus control (Appel & Dykstra, 1977; Heise, 1984; Heise & Milar, 1984; Seiden & Dykstra, 1977).

#### Stimulus Generalization Procedures

While stimulus generalization procedures have generally been used in the analysis of LTM, in the studies reported below they are used to assess drug effects on STM. Only four studies have been carried out looking at the effects of CPZ using stimulus generalization procedures. Key (1961) using a discriminated avoidance procedure trained cats to cross a barrier to avoid a shock in response to a 600 cycles/sec tone and then during extinction tested the cats on tones ranging from 200-2000 cycles/sec. With a single dose of CPZ (5.0 mg/kg), which produced little sedation and no motor deficit, two effects were observed. First, the rate at which the conditioned as well as the generalized responses were extinguished was significantly increased. For example, where previously 11 to 18 sets of tones were required for total extinction of all barrier crossing responses, following CPZ only six to nine were needed. Secondly, although the gradient of generalization remained unaltered the range of tones eliciting barrier crossing responses was markedly reduced. After CPZ the cats failed to respond to auditory stimuli of 200 and 2000

cycles/sec although in the control condition these tones elicited barrier crossing responses for at least the first two of five trials. A similar result was found by Wiltz, Boren, Moerschbaeher, Creed and Schrot (1974) using pigeons whose key pecking was controlled by an array of stimulus lamps. CPZ (dosage approximately 23-75 mg/kg) did not consistently alter the form of the PDG, and it may have reduced the number of responses. The authors comment that this latter result may have been due to the effects of retesting.

The effect of CPZ on the peak shift phenomenon has also been studied. Lyons, Klipec, and Steinsultz (1973) using a line tilt discrimination in pigeons, found that administration of CPZ (10-40 mg/kg) just prior to generalization testing, reduced or eliminated the peak shift in subjects that showed the peak shift in a control generalization test. This result was replicated by Lyons, Klipec, and Eirick (1973) using a floor tilt discrimination in rats. CPZ (1.0-3.0 mg/kg) reduced or eliminated the peak shift in a dose-dependent manner. In both these studies there was no tendency for the discrimination to break down under the influence of CPZ, i.e. the gradient of generalization remained unaltered, although there appeared to be a decrease in the total number of responses, a similar result to that of Key (1961).

These results fit well into the model of CPZ action based on its ability to attenuate the control of stimuli. In a generalization test, the stimuli furthest away from the training stimuli are the weakest and therefore likely to be first affected by CPZ as was found by Key (1961). The attenuation of the degree of stimulus control of the training stimuli in the studies by Lyons et al., (1973a, b,) probably accounts for the lack of peak shift observed due to a decrease in the subjects ability to discriminate the S+ and the S-.

### Discrete-Trials Procedures

The effects of CPZ have been assessed using the successive discrimination (no-delay) procedure, with a variety of stimuli from different modalities, and with a variety of subjects. The procedure appears to have been first used by Blough (1956), where a pigeon faced two semicircular keys that were separated by a vertical partition or bar. A conditional discrimination was established where if the bar was lighted a peck on the dark key was reinforced, and if the bar was dark a peck on the lighted key was reinforced. The effect of CPZ (10 and 30 mg/kg) was to decrease both the total response output and the accuracy in a dose-dependent manner. However the effect was small with the 30 mg/kg dose decreasing the percentage correct by less than 10% (Blough, 1958).

A similar two-lever discrimination was used by Nigro, Fraser and Wade (1967) to establish a brightness discrimination in the rat. The discriminative stimuli were two intensities of a light located above and midway between the levers. When the light was brightly illuminated, a response on the right lever was reinforced and when the light was dimly illuminated, a response on the left lever was reinforced. Accuracy (percent correct) decreased progressively with increasing doses of CPZ (0.25-4.0 mg/kg).

This result is in contrast to that of Meltzer (1965) who found CPZ (3.0-5.0 mg/kg) had no effect on the accuracy of performance in a discrimination task. The results are probably due to differences in the difficulty of the discrimination task between the two experiments. In Meltzer's experiment, stimulus lights were located above each of the two levers and the subject had to respond to the lever below whichever lamp was illuminated. In the study by Nigro et al. the use of a single light meant a more difficult discrimination was involved, therefore the responding was under weaker stimulus control and consequently

affected more by CPZ.

Visual stimuli have been used to assess the effects of CPZ on attention and arousal in monkeys (Pragay & Mirsky, 1973). A successive go-no go shock avoidance procedure was used where responses in the presence of a S+ postponed shock and incorrect responses in the presence of the S- were punished. The effect of CPZ was to increase the initiation time for responses and the authors characterized the effects of CPZ as due to sporadic failures of attention or arousal. Polindora and Urbanek (1964) trained monkeys on a visual discrimination task where they had to detect a visual "pattern" in a background of random visual "noise" to avoid a shock. CPZ (0.25, 0.50, and 1.00 mg/kg) caused a dose dependent decrease in the percentage of signals detected from 80% at 0.25 mg/kg to less than 20% at 1.00 mg/kg.

Ksir and Slifer (1982) used a discrete-trials discrimination procedure to test two levels of stimulus control within a single session. They trained rats to respond to the brighter of two keys to earn reinforcement. Fifty percent of the trials were easy (the incorrect key was not lit) and the other fifty percent were difficult (the incorrect key was dimly lit). CPZ (1.0, 2.0, and 4.0 mg/kg) reduced the percentage of trials on which a response was made for both the easy and difficult trials. At 4.0 mg/kg responses were being made on less than 50% of the trials. The percentage correct decreased for difficult trials at the 4.0 mg/kg dose but there was no decrease in percentage correct at any dose level for the easy trials.

Auditory stimuli were used by Ray and Bivens (1966) who trained rats to perform a conditional discrimination where the subject was presented with two levers and two auditory stimuli (1600 and 400 cps). The subject had to learn that a response on lever A was correct for tone A and a response on lever B correct for tone B. There was little



change in the percentage of control performance at a dose of 1 or 3 mg/kg of CPZ, but the measure fell to 25% at 5 mg/kg and 0% at 7 mg/kg.

The effects of CPZ on shock discrimination has been investigated by several authors. Lloyd, Appel, and McGowan (1978) used a discrete-trials discrimination procedure to determine the effects of CPZ and morphine on the ability of rats to detect shock stimuli. On trials when no shock was presented a left lever press was reinforced and when shock was present a right lever press was correct. On the "shock" trials the intensity varied between 0.05 and 0.10 mA. In the control condition there was a positive relationship between performance and shock intensity on trials where shock was present i.e., as the intensity increased, accuracy increased significantly. CPZ (0.25, 0.50, and 1.0 mg/kg) had no effect on the ability to detect shock of any intensity on trials when the shocks were presented, but on no shock trials the CPZ caused a significant decrement at all shock intensities. The drug also caused a significant decrease in the average time to initiate a trial and the speed of choice responding with differential effects across intensities with the greatest effect occurring at the lowest shock intensity. By comparison morphine, caused a decrease in accuracy on shock trials which the authors interpret as a disruption of sensitivity while they see the effect of CPZ as altering other aspects of discrimination behaviour (response criterion or bias) or attentional processes.

A similar result was found by Hernandez and Appel (1979) using a discrete-trials two choice successive discrimination procedure where rats had to detect either a tone or a weak foot shock embedded in white noise. CPZ (1.0-4.0 mg/kg) produced a decrease in overall discrimination performance due entirely to increasing bias i.e., reporting the presence of stimuli when none were presented. It also

caused a decrease in the speed to initiate trials. When either the tone or the shock was presented the animals given CPZ correctly detected the stimuli. The results support those of Lloyd et al., (1978) and Ksir and Slifer (1982) and suggest the effects of CPZ may be independent of the kinds of stimuli the organism is trained to discriminate. Further the study suggests that CPZ causes a reduction in responding at doses lower than that which have an effect on stimulus control.

Dykstra (1979) trained squirrel monkeys to respond to one lever in the presence of shock and the other lever in the absence of shock. Two discriminations were examined: 35 mA versus no shock and a level of shock near threshold (0.05 or 0.15 mA) versus no shock. CPZ (0.1, 0.17, and 0.3 mg/kg) caused a dose-dependent decrease in accuracy both in the presence and the absence of shock, with no differential effects on the two discrimination tasks.

Other researchers using discrete-trials discrimination procedures have reported that CPZ does not impair the acquisition of discrimination tasks. Using discrimination boxes where rats had to choose the correct door to push open to collect their reinforcement it was found that CPZ had no effect on the rate of learning the discrimination (Feldman, Ellen, Liberson, & Robins, 1959; Lalonde & Vikis-Freibergs, 1982; Sines & Sines, 1958; Telner, Vikis-Freibergs, & Lepore, 1976). However this appears to be the case only when the discriminations are easy or when the CPZ dose is low. Using pigeons, Bloomfield (1972) found that CPZ (5.0 and 10.0 mg/kg) did not impair the acquisition of an easy red/green discrimination but did affect the acquisition of a more difficult left/right discrimination. In addition Sines and Sines (1958), found no discrimination impairment at a CPZ dose of 0.25mg/kg but that 5.0mg/kg produced a marked impairment.

The results of these discrete-trial successive discrimination

studies show that, in general, CPZ produces a dose-dependent decrease in the accuracy of performance. This effect is dependent on the difficulty of the task, with the effect of CPZ being greater as the difficulty of the task increases and as the dose of CPZ increases. In addition, there is some indication that the reduced accuracy caused by CPZ may be due to an effect on bias or response criterion rather than on sensitivity.

#### Delayed Discrimination

There have been several studies conducted assessing the effects of CPZ using zero-delay discrimination procedures. In a study of temporal discrimination, pigeons were presented with a key alternately dark and lighted and were trained to peck when it was lighted. The key was dark for intervals of 3 to 30 seconds. In the first experiment pecking the lighted key was reinforced after short intervals and in the second experiment after long intervals. In the control condition for both experiments the pigeons were able to discriminate the duration of the stimulus with consistently more responses at the reinforced duration. CPZ (2.5 mg/kg) did not abolish pecking but attenuated the discrimination of the duration of the stimulus (Reynolds & Catania, 1962).

Altman, Appel and McGowan (1979) used a two choice discrete-trials procedure in which pigeons were trained to discriminate visual stimuli differing in duration. A peck to the right key after a short (4.5 sec) stimulus or the left key following a long (5.5 sec) stimulus was reinforced. CPZ (7.5, 15.0, and 30.0 mg/kg) caused a dose-dependent decrease in accuracy with performance at the two highest doses significantly different from the control level. The study also looked at the effects on perseveration or response bias. Percent preference was defined as the percentage of responding on the most

frequently reinforced key. The highest dose of CPZ (30.0 mg/kg) produced a change in preference toward the less frequently reinforced key. This dose of CPZ also significantly decreased response speed (where speed is the reciprocal of reaction time).

In a study using pigeons, West, Hernandez, and Appel (1982) noted that previous research had equated response bias with position preference (Altman et al., 1979; Hernandez & Appel, 1979; Lloyd et al., 1978). West et al., (1982) hypothesized that choice behaviour based on some other dimension e.g., colour, would be affected less variably. Pigeons were trained to discriminate two intensities of white light, where a peck on the green side key following the bright stimulus and on the red side following the dim stimulus was reinforced. CPZ (7.5, 15.0, and 30.0 mg/kg) decreased discrimination accuracy for both bright and dim stimuli in a dose-dependent manner and did so in the absence of any decrease in response speed. In addition, no differential effects on the side keys was observed. This finding, of a decrease in accuracy with no change in response bias, agrees with the findings of Altman et al., (1979) and contrasts with the finding that CPZ increases response bias in rats in both shock and tone detection tasks (Hernandez & Appel, 1979; Lloyd et al., 1978). West et al., (1982) suggests that this may represent a species difference, a difference between visual and other types of sensory discriminations or between two-alternative detection as opposed to discrimination tasks.

#### Matching-to-Sample Procedures

Various matching-to-sample procedures have been used in the assessment of drug effects and these studies provide further information on drug effects at the no-delay, zero-delay, and X-delay level. A simultaneous (no-delay) matching-to-sample procedure was used

by Berryman, Jarvik and Nevin (1962) who trained pigeons to peck a centre key illuminated with one of three colours. Following this response the two side keys were illuminated, one with a colour matching that of the centre key the other with one of the other two non-matching colours. All three keys remained illuminated until the bird pecked either of the side keys and an ITI of 25 seconds separated the trials. CPZ was administered in doses of 10 and 20 mg/kg following which the 20 mg/kg dose was repeated and the animals run three hours after the injection.

The results were highly variable with two out of the four birds showing decreased performance at a dose level of 10 mg/kg but only one bird showed decreased performance at 20 mg/kg. When the 20 mg/kg dose was repeated and the animals run three hours after injection, three of the birds showed a deterioration in performance. During all the CPZ tests the response latencies remained within the control values. In the simultaneous matching-to-sample procedure stimulus control is very strong as the choice response is made in the presence of the sample stimulus. This accounts for the finding that performance was not impaired until relatively high doses of CPZ had been administered.

An experiment by Pragay, Mirsky, and Abplanalp (1969) used a zero-delay matching-to-sample procedure with monkeys to study the effects of CPZ, using shock avoidance as the reinforcer. A red-green discrimination was used where the subject had to press the sample key four times within ten seconds and then respond to the choice keys within ten seconds. If these responses were not made within ten seconds the subject's were shocked briefly, as they were for incorrect responses. A new trial began every 20 seconds with the length of the intertrial interval being dependent on the response latency. Four doses of CPZ were administered: 0.075, 0.15, 0.3, and 0.6 mg/kg. In a dose-dependent manner, CPZ had a significant effect on the two

variables assessing psychomotor performance. There was a significant decrease in the omission errors to the sample (failure to perform four responses to the sample key within ten seconds) and in omission errors to the choice (failure to perform a discriminative response within ten seconds). Also there was a paradoxical improvement with CPZ in commission errors (pressing the incorrect key or a non-illuminated key) which the authors explain as being a result of a general decrease in responsiveness. In this zero-delay matching-to-sample procedure the comparison stimuli were presented as soon as the sample stimulus was extinguished. The degree of stimulus control over correct responding would therefore have been high and accounts for the lack of a drug effect on performance accuracy, despite the significant impairment in psychomotor functioning.

#### Delayed Matching-to-Sample

Several studies have looked at the effects of CPZ on DMTS performance. Glick, Goldfarb, Robustelli, Geller and Jarvik (1969) trained monkeys on a matching task where on each trial there was one of five delay intervals: no-delay, 0, 2, 8, or 32 seconds. Stimuli were projected onto a three unit display panel. Under the left and right units there were water delivery tubes and under the center unit there was a "blind" tube. Following projection of a red or green stimulus on the center unit of the display panel the monkey had to touch the blind tube. This would turn on the side stimuli according to whatever delay condition was programmed. A response to the tube under the matching side stimulus resulted in reinforcement with water. CPZ was administered in doses of 0.05, 0.10, 0.20, and 0.40 mg/kg and following each drug trial the monkeys worked continuously for 16 hours and the data was analyzed in eight two-hour cycles.

The results showed that all doses decreased the response rate in

the first cycle with recovery beginning in the second cycle for the 0.05 mg/kg dose and in the third and fourth cycles for all doses except the highest. During recovery the rate became higher than control values indicating a slight rebound or compensation effect. Impairment of accuracy occurred in the first cycle with the greatest decrease in the 0.2 mg/kg condition. No doses caused a significant decrease in accuracy at the 32 second delay condition. Accuracy had generally recovered to baseline levels in cycle two with again some facilitation occurring in cycles three and four. Recovery of accuracy occurred before there was a recovery of response rate. Although statistically significant decreases in accuracy were found, the percentage drop in accuracy was small unless accompanied by a large drop in response rate. The authors concluded that CPZ was not having a specific effect on accuracy.

Robustelli, Geller, and Jarvik (1969) using the same test, the same animals and the same drug doses found that CPZ regularly impaired the response rate without influencing accuracy. In addition since the depressant effect occurred irrespective of the delay the authors argue that no specific effect on STM was involved. Further data on the effects of CPZ on DMTS performance come from a study by Glick and Jarvik (1969) who, while primarily concerned with the effects of drug interactions, also tested a 0.1 mg/kg dose of CPZ alone. The delay conditions and test procedure was the same as in Glick et al., (1969) and a similar pattern of results was obtained. Accuracy was impaired at all delays except 0 and 32 seconds in cycle one, in cycle two all but the 8 second delay condition had recovered and in the third and fourth cycle some facilitation had occurred. The relative response frequency (percentage responses made out of the possible total) showed a significant decrease in cycles one and two with recovery and facilitation in cycles three and four.

Roberts and Bradley (1967) used a go no-go nonmatching procedure to examine the effects of a variety of drugs including CPZ. The subjects were trained to discriminate between red and green illuminations on a response panel. They pressed the panel if the two parts were different colours and refrained from pressing if the same colours were presented. Delays of 0, 3, 5, and 7 seconds were then placed between the two stimulus halves. Control performance showed a decrease in percent accuracy with the increasing delay values. A 2.5 mg/kg dose of CPZ caused a non-significant decrease in accuracy, 4.3%, with the greatest depression in accuracy at 3 and 5 second delays. A 5.0 mg/kg dose of CPZ caused a mean decrease in accuracy of 13.6% which was significantly different from the control values. There was no significant relationship between the length of the delay and accuracy of performance.

### Conclusion

In various discrimination procedures the effect of CPZ appears to be an attenuation of the control exerted by stimuli over appropriate responding. The effect appears to be dose-dependent and also depends of the degree of difficulty of the discrimination task. The results of the delayed matching studies suggests that the performance-by-delay-interval curves for the CPZ conditions were parallel to the control conditions and that there was no differential effect on performance at longer delays as a result of the drug. This implies no specific effect on memory or retention processes.



### CHAPTER THREE

#### Application of the Theory of Signal Detection to the Analysis of Drug Effects

Discrete-trials procedures, including matching-to-sample and conditional discrimination procedures, have advantages in the analysis of drug effects because they avoid the difficulties inherent in the use of response rate to measure drug-behaviour interactions. However, such procedures do not solve the basic problem that a drug's effect on the measure used to evaluate performance cannot be separated from any presumed effect on the ability to perceive and discriminate (i.e., a sensory capacity or threshold) (Appel & Dykstra, 1977; Heise & Milar, 1984; Seiden & Dykstra, 1977). Accuracy on a discrimination task (usually measured using percent correct), may be influenced by two factors. The first is a drug-dependent change in the ability to discriminate the presence or absence of the stimuli (a change in perceptual sensitivity) and the second is a drug-dependent change in the probability that the subject will continue to do on trial  $t+n$  whatever they did on trial  $t$  (an effect on response criterion or bias which is presumed to be independent of ability to detect exteroceptive stimuli) (Appel & Dykstra, 1977).

Some attempts have been made to partial-out the effects of response bias from measures of accuracy or sensitivity using blank trials (i.e., trials in which no stimulus or an irrelevant stimulus is presented) or determining the tendency to respond or not to respond (or to respond right or left) when no sensory discrimination is possible (Seiden & Dykstra, 1977). However, the most systematic and successful attempt to separate the effects of numerous variables on sensitivity from effects on bias has been the application of signal

detection theory (SDT) (Appel & Dykstra, 1977; Heise & Milar, 1984; Seiden & Dykstra, 1977).

### Signal Detection Theory

The theory of signal detection (described in detail by Green & Swets, 1966) was developed as a method for characterizing the discriminative performance of individual human observers and it is widely used in psychophysics. Compared with other classical psychophysical measurement techniques, it has the advantages of separating a subject's bias or response tendencies, which could be influenced by variables such as motivational state, reinforcement magnitude and expectation of reinforcement, from the subject's sensitivity: the ability to discriminate the difference between two stimuli or between a stimulus and background noise. Thus, SDT offers a way to identify separately drug-induced changes in sensitivity (stimulus input) and bias (response output) (Milar, 1981).

In a signal detection procedure, the subjects task is to detect and report whether a stimulus (or signal) has been presented in background noise during a discrete-trials procedure. When a signal versus noise discrimination is made, four possible stimulus-response combinations can occur, as shown in Figure 1. If the subject reports a signal on a trial when a signal has been presented, the response is a hit. A false alarm occurs when a signal is reported on a trial when in fact no signal was presented (a noise-alone trial). Reporting noise when no signal has in fact been presented is a correct rejection and a miss is when the subject fails to report a signal when a signal has been presented.

The model assumes that the signal and noise stimuli each lead to a sensory experience that can be scaled, rated, or ranked on a continuum. The two stimuli each form Gaussian distributions on the

		<u>Response</u>	
		Signal	Noise
<u>Stimulus</u>	Signal	Hit	Miss
	Noise	False Alarm	Correct Rejection

Figure 1. Stimulus-response combinations when a signal-noise discrimination is made.

same continuum. If the signal distribution is well separated from the noise distribution, there will be little or no overlap between the two curves and the discrimination (detection of the signal) will be very easy. However, as the distributions become progressively closer and have a greater degree of overlap, the discrimination becomes correspondingly more difficult. The sensitivity measure,  $d'$ , is intrinsically related to the signal and noise distributions and is equal to the distance between the two distribution means and is measured in Z scores of the noise distribution. By definition:

$$d' = (\bar{X}_s - \bar{X}_n) / \sigma_n \quad (1)$$

where  $\bar{X}_s$  = the mean of the signal distribution

$\bar{X}_n$  = the mean of the noise distribution

$\sigma_n$  = the standard deviation of the noise distribution

The sensitivity measured by  $d'$  can also be determined by the hit and false alarm rates. The probability of a hit is determined by dividing the number of signal responses (S) made to signals by the number of signal presentations (s); false alarm probability is determined by dividing the number of signal responses (S) made to noise stimuli by the number of noise presentations (n). When the signal and noise distributions are Gaussian with equal variance,  $d'$  can be found by subtracting the Z score corresponding to the hit rate from the Z score corresponding to the false alarm rate:

$$d' = Z(S/n) - Z(S/s) \quad (2)$$

Sensitivity is usually a function of the physical characteristics of the stimuli which causes corresponding changes in the overlap of the signal and noise distributions, and of the functional acuity of the receptor systems.

Response-bias is the subject's criterion or decision to report either that noise alone has occurred, or that a signal has occurred. The criterion can fall anywhere on the continuum and is usually

represented by  $B$ , the likelihood ratio (the height of the signal distribution divided by the height of the noise distribution) at the criterion point. If a stimulus exceeds the criterion, the subject will report that a signal has occurred. If the stimulus does not exceed the criterion, the subject will report that a signal has not occurred or that noise alone has occurred. If  $B=1$ , there is no bias, if  $B$  lies between 0 and 1 the subject is biased toward reporting a signal, and if  $B$  is greater than 1 the subject is biased toward reporting that a signal did not occur. Bias is usually a function of the consequences that follow the detection response. The relative outcomes of each of the four possible responses determines the criterion the subject establishes.

Given a large number of trials the probability of a hit can be plotted as a function of the probability of a false alarm in a unit square, and the receiver operating characteristic or relative operating characteristic (ROC) (Swets, 1973) is obtained. If, when the ROC curve is replotted on double probability paper, a straight line with a slope equal to one is obtained, then the assumptions that the signal and noise distributions are Gaussian and have equal variances is met. This means that the sensitivity and bias are statistically independent (Green & Swets, 1966) and the parameters  $d'$  and  $B$  can be used. If the slope is not equal to one, then the sensitivity is probably related to bias and a non-parametric index of sensitivity and bias should be used.

There are two non-parametric models of signal detection theory whose measures are independent of the exact nature of the underlying signal and noise distributions. Grier (1971) devised mathematical expressions for the non-parametric analysis proposed by Pollack and Norman (1964) and Hodos (1970), based on the geometry of the unit square. The area under the ROC curve can be used as a measure of the

sensitivity, and bias is measured by the position of each point on the curve relative to the negative diagonal. Grier's sensitivity measure is:

$$A' = 1/2 + (y-x)(1+y-x) / 4y(1-y) \quad (3)$$

where  $y$  = probability of a hit response

$x$  = probability of a false alarm response

When  $A'$  equals 0.5 the subject is failing to discriminate between the two stimuli (no sensitivity), whereas at an  $A'$  of 1, the subject is perfectly discriminating.

The bias measure is calculated as follows:

$$B'' = y(1-y) - x(1-x) / y(1-y) + x(1-x) \quad (4)$$

where  $x$  and  $y$  are as stated above.

The non-parametric measures provided by Grier have the advantage in that unlike  $d'$  and  $B$ , they can both be calculated when the hit rate is 1.00 or the false alarm rate is 0.

Frey and Colliver (1973) have noted a problem with the use of the  $B''$  measure. They claim that  $B''$  measures the amount of "signalness" a subject requires on a given trial before he will respond i.e., it is a measure of response bias rather than of general bias. The possibility that  $B''$  becomes more "insensitive" to changes in response bias as  $A'$  decreases (Koek & Slangen, 1983) and the finding that  $B''$  varies significantly with increasing sensitivity shown by the subject (Appel & Dykstra, 1977; Robbins & Iversen, 1973), suggests that as a response bias measure,  $B''$  should be interpreted with some caution (Kirk, 1985). Frey and Colliver (1973) derived a general response bias measure called the responsivity index (RI) which is calculated:

$$R.I. = y+x-1 / 1-(y-x)^2 \quad (5)$$

where  $x$  and  $y$  are as above.

A sensitivity index (SI) to measure sensitivity independently of the RI was also obtained:

$$S.I. = y-x / 2(y+x)-(y+x)^2 \quad (6)$$

where x and y are as above.

Two other non-parametric indices of response bias have also been developed, the probability of a yes response / probability of a no response measure (Milar, 1981) and the "probability of response repetition" measure (Koek & Slangen, 1983), but they are not used in this thesis.

### Traditional Signal Detection Analyses of Drug Effects

SDT analyses have been used to assess the effects of a variety of drugs on discrete-trials discrimination procedures. Generally the procedures involve the detection of differences in some stimulus dimension e.g., frequency (pitch), duration, or intensity (brightness). These studies have been reviewed by Heise and Milar (1984). Several studies have used a SDT analysis to examine the effects of CPZ.

Several reports concerning drug effects on discrimination and matching-to-sample procedures have recognized the importance of sensitivity and bias in determining overall performance but have not carried out a formal SDT analysis. For example, Lloyd et al. (1978) and Hernandez and Appel (1979), both using rats, reported that the effect of CPZ was to cause the subjects to report the presence of stimuli (tone or shock) when none in fact had been presented. They interpret this as an effect on bias rather than sensitivity. In contrast, two studies using visual discrimination in pigeons found a decrease in accuracy with no significant change in response bias defined as differential responding on the response keys (Altman, et.al., 1979; West et.al., 1982). Since no formal measures of sensitivity and bias were used in these studies it is difficult to interpret the results.

Other studies have used formal measures of sensitivity and bias to evaluate drug effects. Appel and Dykstra (1977) report a study in which rats were trained to pull a chain to produce either a 2.25 second tone ("signal") or a 1.25 second tone ("noise"). A response on the right lever following the long (2.25 sec) tone and a response on the left lever following the short (1.25 sec) tone were correct and reinforced on every trial. Incorrect responses were followed by a four second time out. CPZ (0.25, 0.50, and 1.00 mg/kg) produced a reliable decrease in the sensitivity ( $d'$ ). This effect was unaccompanied by any change in bias ( $B$ ), i.e., the result cannot be explained by the occurrence of response perseveration or by proposing the existence of deficits in attention or motivation. Essentially the same result was found when pigeons were used in a temporal discrimination procedure (4.5 versus 5.5 sec stimulus duration) and the CPZ doses of 7.5, 15.0, and 30.0 mg/kg were given. Sensitivity ( $d'$ ) decreased significantly, but there was no statistically reliable effect on bias ( $B$ ). Appel and Dykstra (1977) also reported that CPZ (unspecified doses) decreased sensitivity ( $d'$ ) when pigeons worked on a "few" versus "many" discrimination.

In a further study reported by Appel and Dykstra (1977), rats were trained to pull a chain which turned on two red lights located over two levers. On half of the trials the change in illumination was accompanied by a mild shock (signal) and on the other trials the red lights occurred alone (noise). A left lever press in the presence of the shock (signal) was defined as a hit and a right lever press in the presence of the red light (noise) was a correct rejection. Three shock intensities were used: .05, .08, and 1.0 mA and one dose of CPZ (1.0 mg/kg) was tested. The results showed sensitivity ( $d'$ ) decreased at all three shock intensities with the greatest decrease at the lowest shock intensity. Since in the high shock condition performance was



under stronger stimulus control, this result is in agreement with the model of CPZ action that postulates that the drug attenuates the power of stimuli over behaviour.

#### The Behavioural Model of Signal Detection

Recently Mike Davison, Don Tustin, and Dianne McCarthy from the University of Auckland have worked extensively on a behavioural model of detection performance based on an application of the generalized matching law to the standard detection theory payoff matrix. In the standard yes-no detection or two-choice discrimination procedure the subject is trained to emit one response (P1) when one stimulus (S1) is present and another response (P2) when the other stimulus (S2) is presented.

The stimulus-response matrix shown in Figure 2 is obtained. W, X, Y, and Z, refer to the cells of the matrix and if P denotes responses and R reinforcers, P<sub>W</sub> is the number of responses in cell W and R<sub>Z</sub> is the number of reinforcers in cell Z. The matrix is identical to that used in traditional signal detection theory analyses.

Davison and Tustin (1978) conceptualized the discrimination or detection task as two concurrent reinforcement-extinction schedules each operating under a discriminative stimulus. The generalized matching law states that if two stimuli, S1 and S2, are indistinguishable, the distribution of responses over the response alternatives will be determined by the proportion of reinforcers for each response alternative.

$$PA/PB = c (RA/RB)^a \quad (7)$$

Where PA, PB are the number of responses to each response alternative

RA, RB are the number of reinforcers in each response  
alternative

The exponent a is the sensitivity of the response ratio to

		<u>Response</u>	
		P1	P2
<u>Stimuli</u>	S1	Hit	Miss
		H	X
	S2	False	Correct
		Alarm	Rejection
Y		Z	

Figure 2. Two-choice discrimination procedure stimulus response matrix.

changes in the ratio of obtained reinforcements.

c is inherent bias, a constant preference over experimental conditions, unaffected by changes in obtained reinforcement distribution between the two alternatives.

The values of a and c are obtained from the slope and the intercept of a least squares line fitted to the logarithmic data

$$\log (PA/PB) = a \log (RA/RB) + \log c \quad (8)$$

As the stimuli become more discriminable, performance would move toward P1 in S1 and P2 in S2. Davison and Tustin (1978) wrote two generalized matching law equations with an added discriminability term to describe behaviour in the presence of each of the two stimuli.

During or immediately after S1 presentations:

$$\log (Pw/Px) = ar1 \log (Rw/Rz) + \log c + \log d \quad (9)$$

During or immediately after S2 presentations:

$$\log (Py/Pz) = ar2 \log (Rw/Rz) + \log c - \log d \quad (10)$$

Where P and R denote the number of responses emitted and the number of reinforcers obtained respectively and the subscripts refer to the cells of the matrix. The reinforcement ratio  $Rw/Rz$  quantifies a reinforcement bias caused by different numbers of reinforcers obtained across the response alternatives. The parameters  $ar1$  and  $ar2$  measure the sensitivity of response behaviour allocation to changes in the reinforcement ratio in the presence of each of the two stimuli.  $\log c$  represents inherent bias, a constant bias in S1 and S2 that remains invariant across reinforcement and stimulus conditions.  $\log d$  measures the discriminability of the two stimuli.

Like traditional signal detection theory the Davison and Tustin (1978) model separates the effects on behaviour of sensory and non-sensory variables. Discriminability and reinforcement bias have been shown to have independent behavioural effects in that sensitivity to reinforcement ( $ar$ ) does not vary as a function of discriminability

(McCarthy & Davison, 1980b). Therefore equations 1 and 2 can be combined to specify how independent measures of stimulus discriminability and bias can be obtained. Subtracting equation 2 from equation 1 and rearranging gives a bias free point estimate measure of stimulus discriminability:

$$\log d = 0.5 \log (P_w P_z / P_x P_y) \quad (11)$$

Adding equation 2 to equation 1 and rearranging gives a discriminability-free measure of response bias:

$$\log \text{response bias} = 0.5 \log (P_w P_y / P_x P_z) \quad (12)$$

Davison and Tustin (1978) noted that discriminability as in equation 3 was identical to that used by some signal detection theorists (e.g. Luce, 1963) and equivalent to that used by others (e.g. Green & Swets, 1966). The bias measure as in equation 4 is equivalent to the reciprocal of that given by Luce (1963), but the Davison and Tustin measure clearly distinguishes between two sources of response bias:

1. Biases arising from different numbers of reinforcements for the two choice responses
2. A constant bias ( $\log c$ ) which may arise from either the requirements of the experiment (e.g., response production versus response omission; different forces required to operate response manipulanda) or from the subject itself. This constant bias is known as inherent bias.

Both sources of response bias are subsumed under the rubric of "criterion" in signal detection research. The Davison and Tustin (1978) approach is to separate response bias (or criterion) into a variable (i.e., reinforcement) component and a constant (i.e., inherent) component (McCarthy and Davison, 1981). In essence Davison and Tustin showed how independent measures of response bias and discriminability can be obtained from an analysis of detection performance in terms of the matching of response ratios to

reinforcement ratios (McCarthy & Davison, 1981). The model would appear to have two major advantages over previous model of detection or discrimination performance. It is easily able to encompass both intermittent reinforcement for hits and false alarms, and reinforcement for errors, and secondly it makes the role of reinforcement in signal detection clearer (Davison & Tustin, 1978).

Recent research has found that the behavioural model of signal detection accounts well for data obtained in both discrete-trial psychophysical experiments and free-operant multiple-concurrent schedule discrimination tasks. Simple detection performance has been described when either reinforcement parameters, e.g., relative reinforcement frequency (McCarthy & Davison, 1979) and absolute rate of reinforcement (McCarthy & Davison, 1982) or stimulus parameters (McCarthy and Davison, 1980a) have been manipulated. The role of differential reinforcement in detection experiments has been clarified (McCarthy & Davison, 1981) and the importance of a truly bias-free measure of discriminability in threshold studies has been demonstrated (McCarthy, 1983). In addition, the model has provided a quantification of stimulus effects in free operant multiple concurrent schedule paradigms (McCarthy, Davison & Jenkins, 1982).

The Davison and Tustin (1978) model has also been applied to the situation in which a delay is interpolated between the sample and comparison stimuli in a detection or a discrimination task. White and McKenzie (1982) found that  $\log d$  decreased as a negatively accelerated function of increasing delay interval for both single stimulus and relation recall procedures. It was assumed that recallability decremented as a negative exponential function of time,  $t$ , according to:

$$\log dt = \log do.e^{-bt} \quad (13)$$

where  $\log dt$  = the discriminability of the stimuli at time  $t$

$\log d_0$  = the discriminability at  $t = 0$

$t$  = the delay

$b$  = a time constant describing the rate of decrement of  $\log dt$  over time

McCarthy (1981) proposed that rather than the rate of decay being constant as in the negative exponential model, it decreased with increasing delay. McCarthy suggested that the relationship between stimulus discriminability and time is a rectangular hyperbola:

$$\log dt = (h/h+t) \cdot \log d_0$$

where  $h$  = the half life, the time at which discriminability at time  $t = 0$  ( $\log d_0$ ) falls to one half of its initial value.

The two models of discriminability change were compared in a study by Harnett, McCarthy and Davison (1984). Pigeons were trained to peck the red side key when the brighter of two white lights had been presented on the centre key, and the green side key when the duller of two white lights had been presented. The time between the presentation of the sample on the centre key and the onset of the red and green side keys varied nonsystematically from 0.06 seconds to 19.69 seconds across experimental conditions. Stimulus discriminability, as measured by  $\log dt$  decreased as the stimulus choice delay increased. Both the rectangular hyperbolic decay function and the negative exponential model were fitted to the data. Using a criterion of the amount of variance in the data accounted for by the models, both accounted for a high percentage. There was a difference between the models when an analysis was carried out to determine if the slope of the decay function changed between successive data points. The negative exponential model assumes the decay is constant at  $-b$  across all the delay values. The rectangular hyperbolic model states that the decay rate should become less negative (show a positive trend) as the delay ( $t$ ) is increased, and that the decay rate will change faster at

shorter delays. For each bird, the slope/discriminability ratio was calculated for each successive pair of  $t$  values. This ratio became less negative as  $t$  increased for each bird, and in the range  $t=0.46$  to  $t=6$  seconds the slope/discriminability ratio significantly increased. The authors concluded the data were better described by a rectangular hyperbolic model which defines a decreasing rate of decay over time.

Further comparisons of these two models of stimulus discrimination decay were carried out by McCarthy and White (in press) who reanalyzed data from published reports of animal and human memory experiments. In none of the data were bias free measures of  $\log dt$  able to be calculated and McCarthy and White used an alternative discriminability index:

$$\log (\text{no. of correct responses} / \text{no. of errors}) \quad (15)$$

Since this measure is only bias free if the effects of the biaser are symmetric in the two stimuli, data were only chosen for reanalysis if no obvious sources of response bias were present in the procedure (e.g., different reinforcement magnitudes or delays). Further, group data was used in the calculation of the C/E ratios which cancelled out idiosyncratic individual differences.

Several variables were found to have a strong influence on  $\log d_0$  in animal short-term memory experiments including training (Berryman, Cumming, & Nevin, 1963), rehearsal of the sample stimulus (Roberts, 1972), and prior interfering trials (Grant, 1975). The effect of these variables on rate of decay ( $b$ ) and the half-life ( $h$ ) was less clear with rehearsal and possibly prior interfering trials having a significant influence on decay rate.

McCarthy and White (in press) report that in the area of human STM studies, the exponential decay model has been frequently used to quantify the decrease in performance over time (see Wicklegren and Norman, 1966). Reanalysis of an experiment involving delayed

comparison of pitch with human subjects (Wicklegren, 1966) was carried out and the negative exponential and the rectangular hyperbolic decay models fitted to the data. Both models provided good fits to the data, but the hyperbolic model accounted for data in six of the nine comparisons better than the simple exponential model. With long term retention the forgetting rate decreased with increasing delay and while this eliminates a constant decay exponential function for the long delay, McCarthy and White (in press) proposed the hyperbolic model may fit the data. An experiment by Wicklegren and Berian (1971) was reanalyzed and the rectangular hyperbolic model provided a reasonable fit to the data, shown by the small mean square errors of the estimates.

The Davison and Tustin (1978) model therefore provides a good description of delayed response performance in animals and humans. Further the data from animal delayed matching experiments and human STM experiments appears to be described adequately by either the negative exponential or the rectangular hyperbolic decay function whereas human LTM may be best characterized by the rectangular hyperbolic model.

A further analysis of the decay functions in delayed matching-to-sample was carried out by White (1985). In these experiments although the relative frequencies of reinforcers for correct responses could covary with the relative frequencies of correct responses (i.e., an uncontrolled reinforcement rate procedure) the fluctuations in response bias were comparable to those obtained by McCarthy (1983) who used a controlled reinforcement rate procedure. Response bias therefore was practically absent and did not change systematically as discriminations became more difficult with increasing duration of the delay interval.

In Experiment 1, White (1985) examined whether the rate of



decrease in discriminability of the sample stimuli depends on the initial discriminability of the sample stimuli. Two conditions were tested: firstly sample stimuli of 538 and 576 nm with comparison stimuli of 538 and 576 nm and secondly sample stimuli of 501 and 606 nm and comparison stimuli of 538 and 576 nm. The delays between the sample and comparison stimuli were 0.5, 2, 4, 8 or 20 seconds. Data were analyzed using the negative exponential decay model and the parameters  $\log d_0$  (initial discriminability) and  $b$  (the rate of decay) were examined. It was found that a large difference between wavelengths of the sample stimuli resulted in a higher  $\log d_0$  value than for the small difference between the wavelengths but that the rate of decrement in discriminability,  $b$ , was the same in both cases. This result is similar to that obtained by White and McKenzie (1982) who found that  $\log d_0$  was smaller for a difficult discrimination between the stimulus relations of "same" and "different" than for an easier discrimination between sample stimuli with very different wavelengths.

A second experiment by White and McKenzie (1982) had found  $\log d_0$  was smaller when the sample stimuli had similar wavelengths than when the wavelengths of the sample stimuli were widely separated - a similar result to Experiment 1 by White (1985). In both experiments by White and McKenzie (1982) there were no systematic changes in values of  $b$ , and White (1985) concluded that changing the  $\log d_0$  value of the sample stimuli by changing their separation on some stimulus dimension does not change the rate at which discriminability diminishes as the duration of the delay increases.

White (1985) also proposed the possible independence of the two characteristics of forgetting functions that the negative exponential decay model provides i.e., the initial discriminability,  $\log d_0$ , and the rate of decay,  $b$ . In Experiment 2, variables addressing the main

features of the DMTS procedure (i.e., sample stimulus parameters, delay interval conditions and the intertrial-interval conditions) were examined to determine their effects on log  $d_0$  and  $b$ . The variables were the fixed ratio requirement for sample key responding, the duration of the ITI and the inclusion of ambient illumination (from the houselight) during the normally dark delay interval.

The results showed that decreasing the ITI from 20 to 5 seconds caused a significant decrease in the log  $d_0$  values and although  $b$  was greater in the 5 second than 20 second condition, the difference was not significant. However the author comments that unpublished data showed an increase in  $b$  with decreasing duration of the ITI and cautioned that the impact of ITI on  $b$  should not be disregarded.

A comparison of FR1 versus FR5 response requirements on the sample stimulus showed a higher log  $d_0$  estimate for the FR5 requirement and no significant difference in the rate of decrement in discriminability. Interpolation of the houselight in the normally dark delay interval reduced discriminability at long delays but had little effect at the shortest delay. There was no effect on log  $d_0$  but there was a large increase in  $b$ , the rate of decrement in discriminability. Data from two conditions when the houselight was turned on 2 or 4 seconds into the delay showed that the levels of discriminability at the longer delays, given that the latter part of the delay was illuminated, were independent of whether the initial portion of the delay was dark or illuminated.

In summary, the behavioural model of memory differs from previous accounts of memory functioning. For example White (1985) comments that, in accounting for the interference effects by stimuli from past trials, the effect of the inter-trial interval duration has more to do with discriminating the sample stimuli than with post-sample or "memorial" processes as is assumed by the trace-strength theory

(Roberts & Grant, 1976) or by its subsequent revision (Grant, 1981a).

### The Behavioural Model of Signal Detection and the Analysis of Drug Effects

The measures derived from the matching model of signal detection would appear to have certain advantages in the analysis of drug effects. They provide a means to quantify changes in performance allowing comparisons across baseline and drug conditions. The aim of this thesis was to apply the measures derived from the behavioural model of signal detection to an analysis of the effects of two drugs, chlorpromazine and haloperidol. The measures derived from the behavioural model will be compared with traditional non-parametric models of signal detection performance. The data obtained will provide a further means of evaluating the behavioural model of signal detection and will provide a test of the two-component process of memory proposed by White (1985). Finally, the analysis will allow the development of models of drug action that will make particular reference to drug effects on discrimination and memory processes.

## CHAPTER FOUR

### A Signal Detection Analysis of the Effects of Chlorpromazine on Remembering

#### Experiment 1

The aim of this experiment was to assess the effects of CPZ on DMTS performance in pigeons. The DMTS procedure was used because of the advantages discrete-trials procedures have in the assessment of discrimination and memory processes. In addition, the extensive theorizing concerning pigeon memory is based on experiments carried out using the DMTS procedure. The experimental procedure used was such that the data produced would allow for several forms of analysis: conventional non-parametric signal detection analysis; the application of the behavioural model of signal detection; and an analysis of the decay functions. It has been suggested by Logue (1983) that a signal detection analysis is more efficient for examining changes in the difficulty of a discrimination, whereas a matching law analysis is more effective for examining the effects of biasers on responses, such as different frequencies of payoffs on responses.

In this experiment it was necessary to maximize the subjects performance during baseline to allow performance to vary between high baseline levels and chance levels, so drug effects would be apparent and not masked by floor effects. Various experimental parameters of the DMTS procedure were manipulated to maximize the subjects performance prior to drug administration. The response requirement on the centre key was a FR5 as this has been shown to enhance performance compared to a FR1 schedule, for example. A relatively long ITI (15 seconds ) separated the trials as this has also been shown to enhance

performance. The delay intervals between the sample and comparison stimuli and also the ITI's were spent in darkness to prevent the disruption of performance by the interpolation of illumination cues (White, 1985). The delay values in this experiment were varied within each session as White and Bunnell-McKenzie (1985) have shown that remembering depends on the temporal context provided by the delay intervals. They found the accuracy of MTS was higher overall with variable delays than with delays where the interval was fixed during the session. Since the effect of CPZ was to be assessed across a variety of delay values in this experiment, and baseline performance needed to be maximized, variable delays within each session were used. This has the further advantage of ensuring that the assessment of performance in each session or phase, at each delay is aggregated over the same set of experimental sessions.

To minimize the likelihood that position or colour biases would occur, a controlled reinforcement rate procedure was used. In most detection or MTS procedures uncontrolled reinforcement rate procedures are used. There is usually continuous or probabilistic (variable ratio) reinforcement scheduling, where the relative frequency of reinforcers obtained for the two choices can vary with the subjects behaviour. Any biasing variable in the situation causes an inequality between the numbers of reinforcements obtained for the choice responses and this leads to a further change in the response proportions. Overtime, responding will, in the limit, become exclusive to one choice. The more discriminable the stimuli are, the slower this change will occur. If bias is a function of obtained reinforcement ratio and not the signal presentation probability, as was argued by McCarthy and Davison (1979), then a constant measure of bias can only be obtained from a procedure which controls the reinforcement ratio. Controlled reinforcement rate procedures are those in which changes in

preference can not alter the relative distributions of reinforcers for the two response alternatives. They can be set up by having the correct side key responses reinforced according to two non-independent concurrent variable interval schedules.

In the uncontrolled reinforcement rate situation, as stimulus values (or differences) decrease, behaviour moves from being under the control of stimuli (at high discriminability levels) to control by the reinforcers (at low discriminability levels). In a controlled reinforcement rate procedure, behaviour is always under the joint control of both the discriminative stimuli and the reinforcers along the entire stimulus dimension. McCarthy (1983) compared both controlled and uncontrolled reinforcement rate procedures in a task where pigeons were trained to detect luminance changes. Extreme response biases developed as luminance was decreased to threshold levels in the uncontrolled reinforcement procedure. In the controlled reinforcement rate procedure, there were no progressive changes in response bias as a function of decreasing luminance levels. In a delayed detection experiment where a controlled reinforcement rate procedure was used (Harnett et al., 1984), response bias did not deviate significantly from zero bias as the delay interval was increased. Approximately equal numbers of reinforcers were obtained on the two response alternatives, and in the absence of any inherent bias the response bias values were close to zero. In addition, response bias has been found to remain constant as the discriminability decreases (Harnett et al., 1984; McCarthy, 1983; McCarthy & Davison, 1984).

In this experiment, a dose-response relationship for chlorpromazine was determined using delay intervals up to 16 seconds. It was hypothesized that chlorpromazine would cause a decrease in discriminability but that this would occur independently of any

changes in bias. In addition, past research suggested that chlorpromazine has no differential effect on performance as the delay interval increased. Therefore, it was hypothesized that chlorpromazine would affect only the initial discriminability value,  $\log d_0$ , and not the rate of decay,  $b$ , or the half-life,  $h$ . As the dose increases, the decrement in the initial discriminability will be greater. The experiment will also compare the indices of discriminability and bias used in the behavioural model of signal detection with traditional non-parametric measures and assess the effects of CPZ on measures of psychomotor performance.

## Method

### Subjects

Five experimentally naive homing pigeons obtained from local suppliers were used as subjects. All subjects were maintained at  $80\% \pm 15g$  of their free feeding body weight by supplementary feeding of grain in the home cage after each experimental session. Each subject was individually housed with unlimited access to water and grit in a room with constant temperature ( $24^\circ C$ ), with lights on from 6 a.m. to 6:30 p.m. The subjects were numbered from 1 to 5.

### Apparatus

Two Gerbrand (Model E3125AA) pigeon station operant conditioning chambers were used. The chambers measured 50.5 cm deep, 50.5 cm high and 20 cm wide. Three response keys, 2.5 cm in diameter, were located on the intelligence panel, 8 cm apart and 23 cm from the bottom. These keys could be illuminated with white, red or green light. A minimum of 20g pressure was required for key operation. A centrally located aperture 6 cm from the floor gave access to a hopper filled with grain.

When raised the food hopper was illuminated with a white light. An exhaust fan supplied masking noise and ventilation to the chambers.

In addition two wooden chambers, constructed to the same dimensions as the standard pigeon chambers, were used. Since the chambers were slightly different the subjects worked in the same chamber throughout the training and subsequent experimental phases of the study.

A PDP 11/10 computer, running software written locally for these experiments, was used to control the experimental events and collect the data.

### Behavioural Procedure

Training. Throughout initial training and subsequent experimental phases of the study, the subjects were run, one session per day, at approximately the same time each day, seven days a week. They were initially magazine trained to eat grain from the raised and lighted food hopper and were then autoshaped (Brown & Jenkins, 1968) to peck the centre key when it was illuminated with white light to obtain 3 seconds access to food. Key pecks were initially reinforced on a continuous reinforcement schedule, then on a FR-5 and then a FI-25 sec schedule.

A discrete-trials procedure was then introduced. Daily sessions involved 72 trials with an ITI of 25 seconds, during which pecks on any key had no programmed consequences. Initially the subjects were trained to match a single colour. A red or green sample stimulus was presented on the centre key, and following five pecks the sample was extinguished and one of the side keys was illuminated with the same colour (comparison stimulus). A peck on the illuminated matching side key (a correct response) was reinforced with food presentation and a peck on the unilluminated side key (error) produced a 3 second



blackout. Both the colour of the sample stimulus and the position of the comparison stimulus was randomized across trials. When all subjects were reliably responding with 90-95% correct, the zero-delay MTS was introduced.

The zero-delay MTS procedure was as follows. Each trial was initiated with the illumination of the centre key with one of two colours (red or green). Five key pecks extinguished this sample stimulus and immediately illuminated both side keys, one red and one green. A single response on the matching side key (a correct response) was reinforced with food presentation (3 seconds) and a single response on the nonmatching side key (an incorrect response) produced a 3 second blackout. The colour of the sample stimulus and the position of the matching comparison stimulus (left or right) was randomized across the trials to ensure the percentage of correct responses obtained was conditional on the colour of the sample stimulus. Each trial was followed by a 25 second ITI and each daily session had 72 trials. When accuracy on the zero-delay MTS procedure reached 90-95% correct for each subject, delays were interpolated between the sample stimulus being extinguished and the comparison stimuli being illuminated.

Initially a very short delay (1 second) was introduced on 12 of the 72 trials in each session. This caused a decrement in performance and further delay values were not introduced until the subjects performance was reliably back to 90-95% correct. Gradually six delay values were introduced across the trials in each session. These values were: 0, 1, 2, 4, 8, and 16 seconds. Eventually each session of 72 trials contained 12 trials at each of the delay values. Delay values were assigned to trials on a random basis. After extensive training on this procedure (2-3 months) the subjects were reliably attaining an overall accuracy of 80-90% correct on the DMTS procedure.

The Experimental Procedure. The DMTS procedure used during the training period was an uncontrolled reinforcement procedure. Some of the subjects during training did develop extreme position biases because the procedure allowed them to respond exclusively on one side key and still obtain 50% of the available reinforcers. To prevent such biases a controlled reinforcement rate procedure was introduced. Each session contained 120 trials, 20 at each of the six delay values (0, 1, 2, 4, 8, and 16 seconds). The distribution of the sample stimuli (red and green) on the centre key was random with the exception that no more than 3 consecutive stimuli could be the same colour. The distribution of the comparison stimuli colours on the side keys (i.e., red-left and green-right or green-left and red-right) was random except that on no more than 3 consecutive trials was the same colour in the same position. In addition, for no more than 3 consecutive trials was the correct "matching" comparison stimulus on the same side key. Reinforcers were distributed on a VR-2 schedule. Non-reinforced correct trials had the same consequence as errors i.e., a 3 second blackout as it had been shown that discriminability was unaffected by such a procedure (McCarthy & Davison, 1982). On no more than 3 consecutive trials were reinforcers earned by the subjects. The reinforcement schedule was arranged so that a subject who attained 100% correct would receive exactly 60 reinforcements. A subject with an exclusive colour or position bias would receive a maximum of 30 reinforcements per session. The delays across the trials were randomly distributed with no more than three delays of the same interval on consecutive trials. The presentation of the hopper when reinforcements were earned was for 2.5 seconds and the ITI was 15 seconds. Sessions continued until the 120 trials had been completed or 90 minutes had elapsed, whichever came first.

The subjects continued to work on this procedure until they met two stability criteria (Harnett et al., 1984). The first was that the median proportion correct responses over five sessions be within 0.05 of the median from the preceding five sessions. This criterion had to be met five, not necessarily consecutive, times by each subject. The second criterion was that there be no increasing or decreasing trend in the value of log d for each subject over consecutive training sessions.

#### Pharmacological Procedure

Four doses of CPZ were tested: 0.5, 2.5, 5.0, and 12.5 mg/kg. The drug was obtained from commercial suppliers in 25 mg/ml, 1 ml ampoules. The drug was diluted with isotonic saline and solutions of four concentrations were prepared: 0.5, 2.5, 5.0, and 12.5 mg/ml. Each subject was given three administrations of each dose in a random order. On the day immediately preceding each drug injection, a vehicle control injection was given (isotonic saline). All injections were given in a volume of 1 ml/kg, intraperitoneally, 15 minutes prior to the experimental session. Between each drug injection and the next vehicle control injection there were at least two washout days. The proportion correct had to be within 0.05 of the mean proportion correct during baseline before the next injection was administered.

Following this initial series of 12 drug trials each subject then received a further three administrations of a higher dose of CPZ, 15 mg/kg.

#### Results

Two groups of variables were assessed to determine the effect of vehicle control and drug injections. Psychomotor performance was

assessed using measures of response failure, centre key latency (CKL), and side key latency (SKL). Matching performance was assessed using (for both analyses) discriminability and response bias measures obtained from the behavioural model of signal detection (Davison & Tustin, 1978). In addition, for the analysis of the effects of CPZ, two non-parametric indices of discriminability and response bias were calculated (Frey & Colliver, 1973; Grier, 1971). The determination of all of the indices derived from signal detection theory involves casting the data into a signal detection matrix. Calculation of the indices in the behavioural model of signal detection requires at least one entry in all four cells of the matrix. The performance of most of the subjects at short delay values was high and often there were zero entries in the error cells (i.e., the miss and false alarm cells) of the matrix. Therefore the data were pooled across the subjects at each delay value for each condition. In this "group" data there were generally sufficient errors to enable calculation of the indices even at the zero delay level.

Although the non-parametric indices of discriminability and bias can be calculated when the probability of a false alarm or a miss is zero, Kirk (1985) pointed out that the bias scores in particular fluctuate widely between extreme values when performance is near perfect. Therefore, non-parametric indices were not calculated when there were no misses or false alarms in the group data.

The results from the analysis of the vehicle control injections will be presented first, followed by the analysis of the effects of chlorpromazine. Data from individual subjects for a "composite" drug condition will be presented and finally an analysis of baseline performance before and after exposure to the drug is given.

#### The Effect of Vehicle Control Injections on Performance

Twelve vehicle control injections were administered. These 12 sessions were divided into conditions according to which drug dose the vehicle control injections preceded. Only the drug doses in the first randomized design, i.e. up to 12.5 mg/kg, were used to determine the saline conditions. Therefore there were four vehicle control conditions: saline prior to 0.5 mg/kg (S0.5 mg/kg), saline prior to 2.5 mg/kg (S2.5 mg/kg), saline prior to 5.0 mg/kg (S5.0 mg/kg), and saline prior to 12.5 mg/kg (S12.5 mg/kg). These four vehicle control conditions were compared to a baseline condition formed by pooling the data from the last three days of the baseline period.

Measures of Psychomotor Performance. Several variables were used to assess the effects of the vehicle control injections on psychomotor performance. The first of these was response failure. This occurred when a subject did not complete all the 120 trials in a session. In baseline and all of the saline conditions, there was no response failure, with all five subjects completing all 120 trials per session.

The centre key latency (CKL) was defined as the time to complete five effective key pecks on the sample stimulus. For each session the median latency was calculated for each delay value. The mean of these median values was calculated across all sessions in the conditions for each subject. The mean CKL values across all subjects is presented in Table 1. A two-way repeated measures analysis of variance (Lane, 1981), showed there was no significant effect due to the conditions factor or the delay factor.

The side key latency (SKL) was defined as the time between the comparison stimuli becoming illuminated and the animal responding to extinguish the lights. The mean SKL values at each delay across the conditions is presented in Table 2. Again an analysis of variance showed there was no significant effect due to either the conditions or

Table 1

Mean Centre Key Latency (sec) Across Baseline and Saline  
Conditions for Each Delay Interval

Delay	Condition				
	B	S0.5	S2.5	S5.0	S12.5
0	2.68	2.62	2.42	2.52	2.48
1	2.54	2.87	2.42	2.51	2.52
2	2.51	2.61	2.55	2.53	2.44
4	2.72	2.64	2.36	2.59	2.42
8	2.59	2.85	2.49	2.59	2.45
16	2.71	2.64	2.57	2.59	2.80

Table 2

Mean Side Key Latency (sec) Across Baseline and Saline  
Conditions for Each Delay Interval

Delay	Condition				
	B	S0.5	S2.5	S5.0	S12.5
0	1.45	1.32	1.32	1.29	1.33
1	1.41	1.32	1.32	1.36	1.30
2	1.34	1.31	1.28	1.34	1.29
4	1.51	1.50	1.38	1.31	1.28
8	1.40	1.43	1.47	1.41	1.50
16	1.53	1.49	1.45	1.46	1.48

the delay factor.

Bias. A controlled reinforcement rate procedure was used to prevent the development of bias in the subject's responding. To calculate both the bias and the discriminability indices from the behavioural model of signal detection, the number of responses made to the red and green comparison stimuli following red and green sample stimuli was determined. Data for the baseline and vehicle control conditions are presented in Table 3. A bias value for each delay and each condition was calculated using equation 12 (see Chapter Three).

The bias values for each delay and each condition are presented in Figure 3. At zero delay for baseline and at zero and one second delay for the vehicle control conditions, there were insufficient entries in the "error cells" of the signal detection matrix to allow a bias value to be calculated. When there are zero entries in one of the cells the matrix, a bias value can not be determined. In Figure 3 the solid line indicates zero bias (where errors are equally distributed across the red and green comparison stimuli). Points above the line indicate a bias toward responding to the red comparison stimulus and points below the line, indicate a bias toward responding to the green comparison stimulus. Figure 3 shows that across all conditions response bias values were close to zero for all delay values. As a group the subjects showed a modest tendency to respond to the red comparison stimulus. Of the 21 bias values, 76% were positive indicating a consistent, but negligible bias to respond to the red comparison stimulus.

Discriminability. The values for the bias-free measure of discriminability,  $\log d$ , were calculated using equation 11 (see Chapter Three). The values for each delay and each condition are



Table 3

Number of Red and Green Comparison Key Responses  
Following Red and Green Sample Stimuli for the  
Baseline and Saline Conditions

Condition Delay		C. R. GG	F. A. GR	Miss RG	Hit RR
B	0	150	0	1	149
	1	142	8	2	147
	2	142	8	10	140
	4	132	18	11	139
	8	115	35	27	123
	16	99	51	29	121
S0.5	0	150	0	0	150
	1	148	2	0	150
	2	149	1	3	147
	4	135	15	11	139
	8	116	34	28	122
	16	103	47	39	111
S2.5	0	150	0	0	150
	1	150	0	0	150
	2	149	1	1	149
	4	147	3	8	142
	8	112	38	25	125
	16	97	53	49	101
S5.0	0	150	0	0	150
	1	145	5	0	150
	2	146	4	6	144
	4	137	13	10	140
	8	129	21	20	130
	16	104	46	34	116
S12.5	0	149	1	0	150
	1	149	1	0	150
	2	149	1	2	148
	4	139	11	10	140
	8	122	28	30	120
	16	102	48	32	118

C. R. = Correct Rejection

F. A. = False Alarm

LOG RESPONSE BIAS

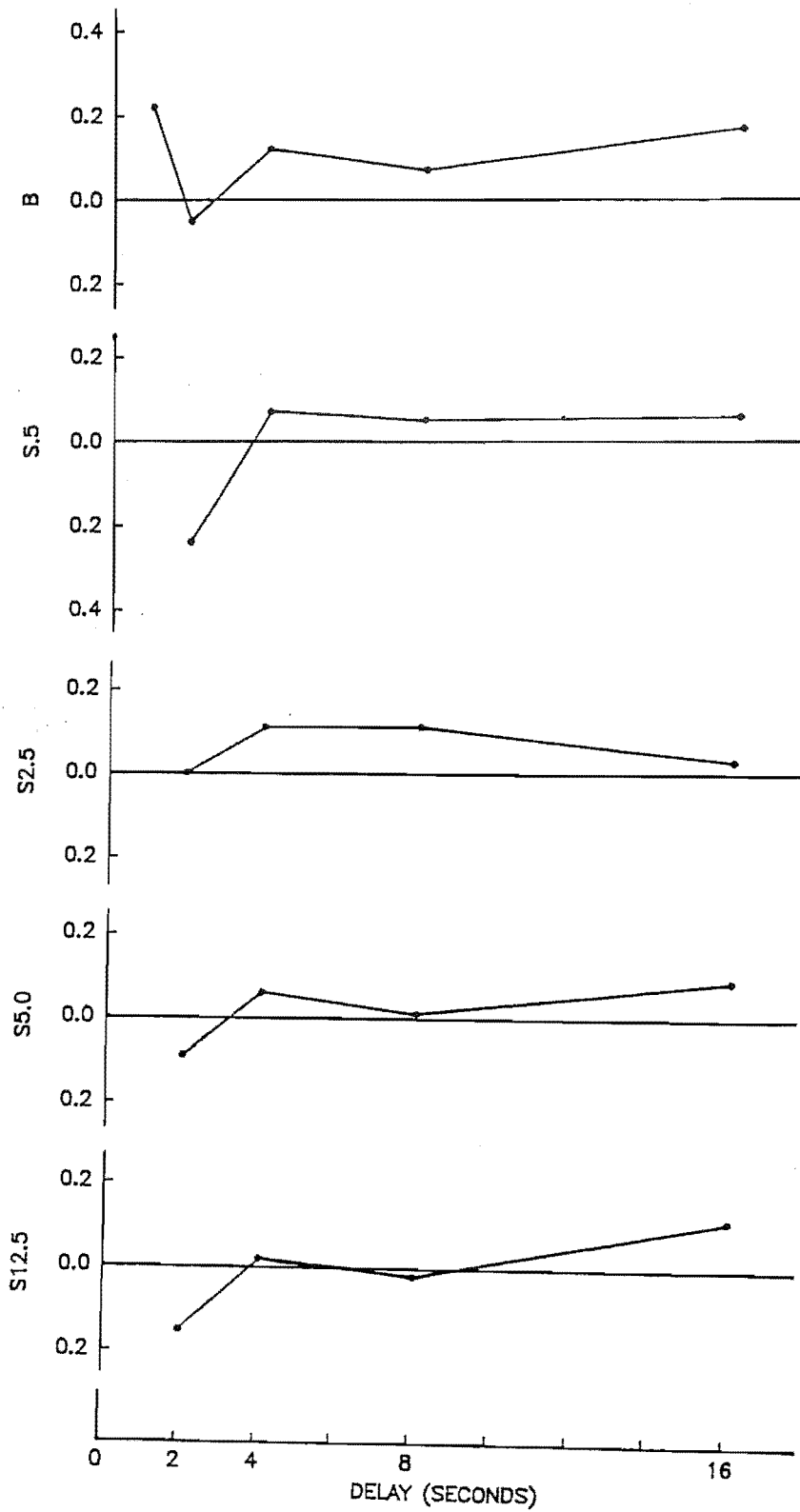


Figure 3. Point estimates of log response bias for the baseline and saline conditions.

presented in Figure 4. Again values for the shortest delays in some conditions were unable to be calculated. The value of log d decreased as the delay interval increased, with the greatest decreases in discriminability occurring between a value of 2 and 4 seconds. Discriminability was greater in all of the vehicle control conditions than in the baseline condition. There was greater variability in the vehicle control conditions at the shorter delay values than at the 8 and 16 second delays. It is not possible to carry out an analysis of variance on these data as a value for log d cannot be calculated for each subject. However since bias was close to zero, log d and percent correct were highly correlated ( $r = .92$ ), so the percent correct data were used in the analysis of variance, since a value for percent correct was able to be calculated for each subject.

Percent Correct. The percentage of trials on which correct matching responses were made was calculated for the baseline and saline conditions. The data are presented in Figure 5. The percent correct data show less variability than the discriminability data and there was an obvious ceiling effect at the short delays that was not apparent in the discriminability data. Performance was again high until a delay interval of 4 seconds was reached. To test for any significant differences in the percent correct due to either increasing delay or the conditions factor, a two-way repeated-measures analysis of variance was run, using Lane's programme (Lane, 1981). The data were first transformed using the arc sine transformation (Winer, 1962) to normalize the data.

There was no significant effect due to the conditions factor but the delay factor was significant  $F(2,10) = 64.13$ ,  $p < .01$ . [Note the degrees of freedom have been corrected by multiplying by the epsilon value which helps to correct for deviations in the assumptions

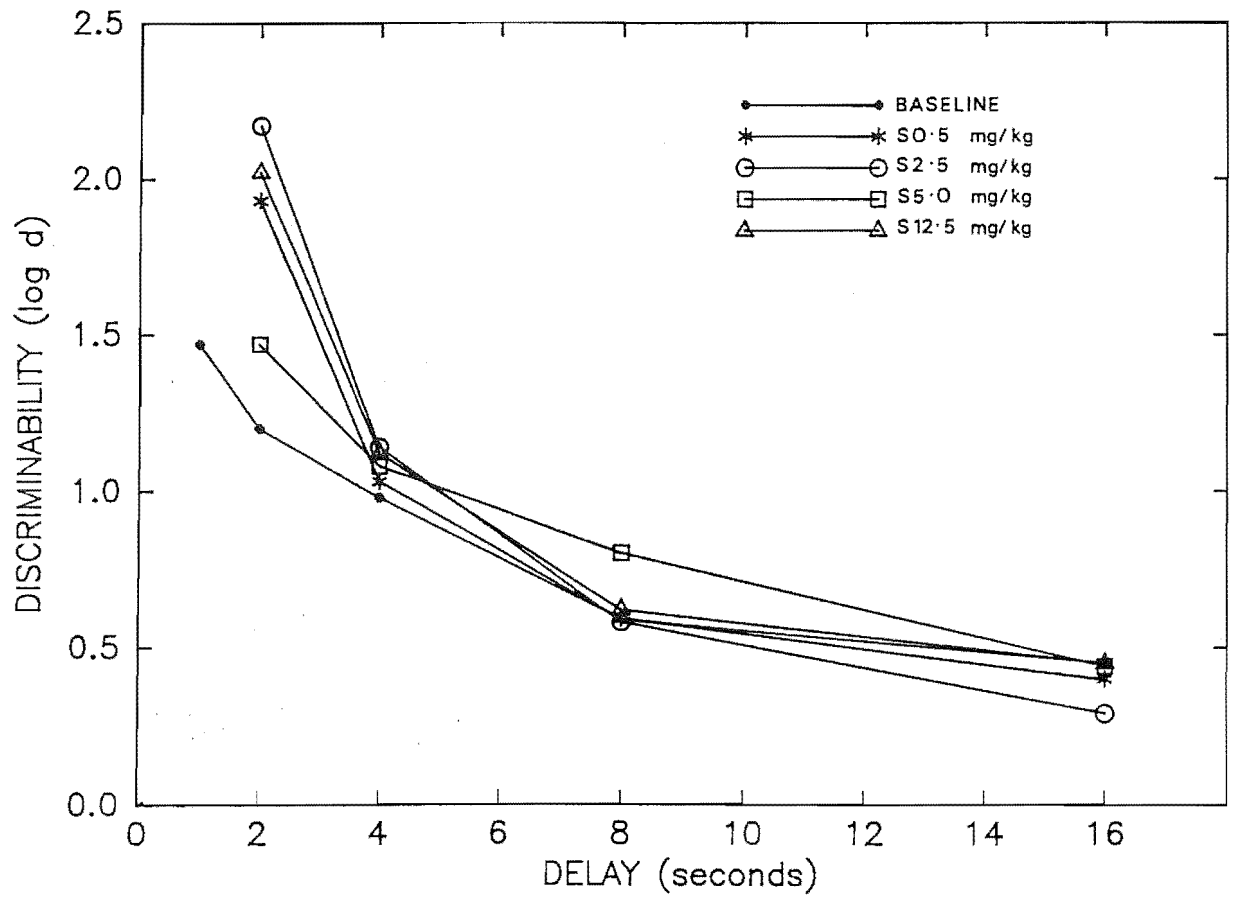


Figure 4. Point estimates of discriminability for the baseline and saline conditions.

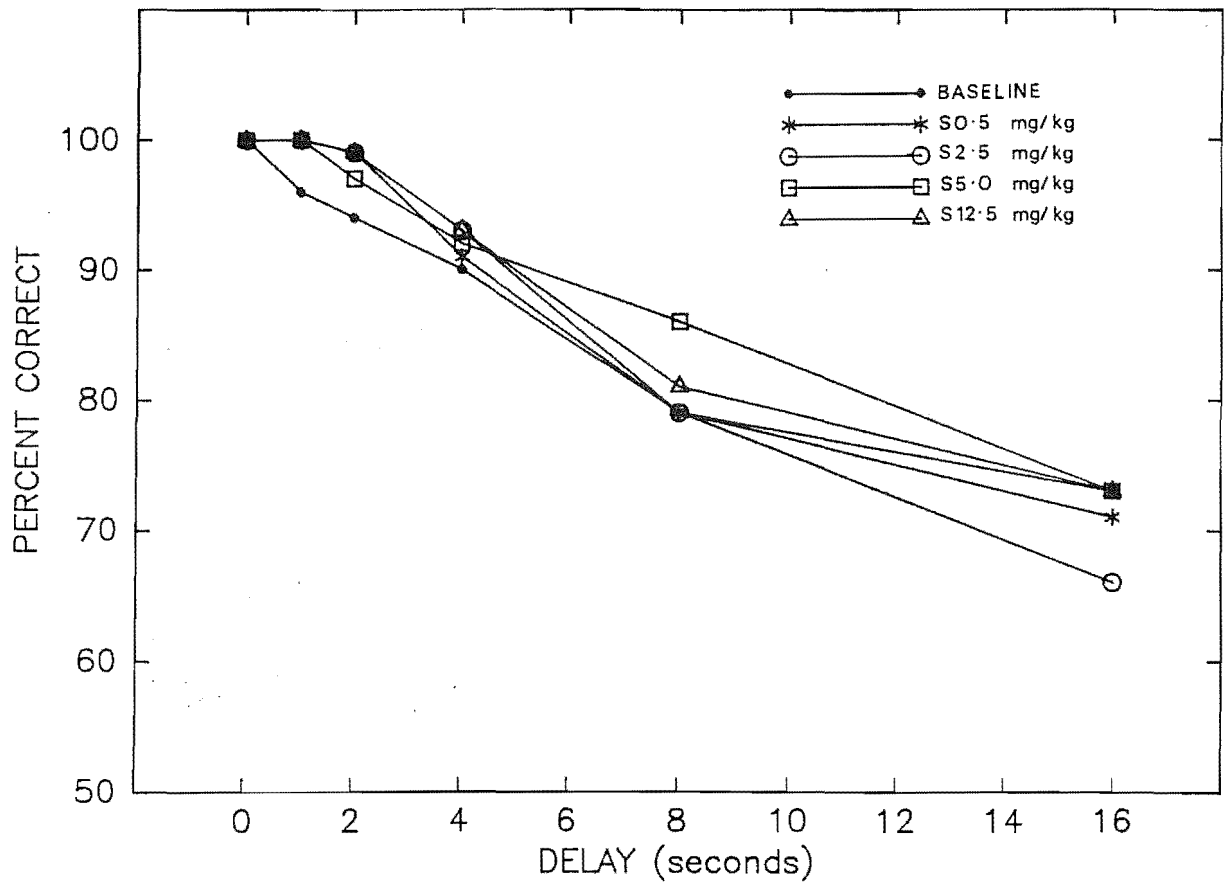


Figure 5. Percent correct for the baseline and saline conditions.

underlying the repeated measures analysis of variance (Huynh, 1978). All subsequent analyses of variance using percent correct data have been carried out in the same way]. In this case as the delay increased, there was a significant decrease in the percentage of trials on which correct matching occurred. There was no significant interaction between the condition and delay factors.

Since the vehicle control injections had no significant effect on either psychomotor or matching performance, the data from three days on which vehicle control injections were given, chosen at random, were collated to form composite saline scores on all variables. The characteristics of this composite saline condition are presented in Table 4.

The percent correct and log d values for the composite condition are close to the mean values across the saline conditions and are slightly higher than the baseline values. These composite scores were then used as the control against which performance in the drug conditions was assessed.

#### The Effects of Chlorpromazine on Performance

Measures of Psychomotor Performance. There was no response failure during the composite saline condition or any of the drug conditions up to and including 12.5 mg/kg. At the 15 mg/kg dose, subject number 4 completed 84% of the available trials and subject number 3 completed just 4% of its available trials. The mean centre key latency across drug conditions for each delay is presented in Table 5. The mean side key latency for each drug condition across the delay values is presented in Table 6.

Although for both the centre key latency and side key latency data the means increased with the increasing delay interval and with

Table 4

Characteristics of the Composite Saline Condition

Delay	Percent Correct	Log d	Bias
0	98	1.78	-.09
1	99	1.93	.24
2	98	1.82	-.36
4	92	1.08	-.02
8	82	.67	.05
16	74	.47	.19

Table 5

Mean Centre Key Latency (sec) Across Composite Saline  
and Drug Conditions for Each Delay Value

Delay	Dose (mg/kg)					
	S	0.5	2.5	5.0	12.5	15.0
0	2.57	2.10	2.64	2.42	2.87	2.53
1	2.41	2.16	2.75	2.39	2.88	2.43
2	2.53	2.54	2.71	2.38	2.73	2.62
4	2.44	2.57	2.56	2.46	2.85	2.70
8	2.53	2.50	2.61	2.43	2.83	2.95
16	2.87	2.51	2.64	2.45	2.87	3.00



Table 6

Mean Side Key Latency (sec) Across Composite Saline and  
Drug Conditions for Each Delay Value

Delay	Dose (mg/kg)					
	S	0.5	2.5	5.0	12.5	15.0
0	13.4	12.6	12.7	12.8	13.9	13.3
1	13.4	13.0	13.0	13.5	15.3	13.3
2	13.8	13.9	13.4	13.8	15.5	17.4
4	14.5	14.6	13.9	14.3	15.0	14.0
8	15.1	13.7	14.3	14.1	15.8	16.7
16	15.1	14.7	14.6	14.9	17.7	16.5

the increasing drug dose, an analysis of variance showed that in both cases there was no significant effect due to either the delay factor, the drug condition factor, or their interaction. The analysis of variance was performed on data up to and including the 12.5 mg/kg condition. The 15 mg/kg condition data was excluded as it was not collected as part of the randomized design.

Bias. The data used in the calculation of the point estimates of bias and discriminability, i.e. the number of responses made to the red and green comparison stimuli following red and green sample stimuli, are presented in Table 7. The point estimates of bias obtained for each condition across the delay values are presented in Figure 6.

In this data set there were insufficient errors at the zero second delay interval for the 0.5 mg/kg dose level to allow estimates of bias and discriminability to be calculated. As can be seen in Figure 6 all the values were close to zero, represented by the solid line, for each of the drug conditions. Again in the majority of cases (62%) the bias values were toward responding on the red comparison stimulus. This was particularly so for the two highest drug conditions.

Discriminability. The point estimates of discriminability,  $\log d$ , at each delay for each condition are presented in Figure 7. Discriminability decreased as a function of the delay value for all conditions. In the composite saline condition performance remained high until a delay value of 2 seconds, then rapidly decreased at the 4, 8, and 16 second delay values. Performance also decreased as a function of the drug dose. Performance at all drug doses was lower than performance in the composite saline condition, with performance

Table 7

Number of Red and Green Comparison Key Responses  
Following Red and Green Sample Stimuli for  
the Composite Saline and Drug Conditions

Dose (mg/kg)	Delay	C. R. GG	F. A. GR	Miss RG	Hit RR
S	0	148	2	3	147
	1	147	3	1	149
	2	149	1	5	145
	4	139	11	12	138
	8	121	29	24	126
	16	98	52	27	123
0.5	0	150	0	0	150
	1	142	8	3	147
	2	146	4	9	141
	4	129	21	16	134
	8	123	27	39	111
	16	109	41	39	111
2.5	0	145	5	5	145
	1	143	7	10	140
	2	142	8	5	145
	4	120	30	26	124
	8	99	51	55	95
	16	90	60	52	98
5.0	0	145	5	1	149
	1	143	7	15	135
	2	136	14	18	132
	4	130	20	27	123
	8	108	42	51	99
	16	96	54	51	99
12.5	0	133	17	4	146
	1	124	26	9	141
	2	116	34	22	128
	4	100	50	28	122
	8	90	60	44	106
	16	77	73	59	91
15.0	0	103	12	1	114
	1	97	16	8	109
	2	89	25	10	106
	4	72	44	14	103
	8	69	49	33	86
	16	61	58	32	86

C. R. = Correct Rejection

F. A. = False Alarm

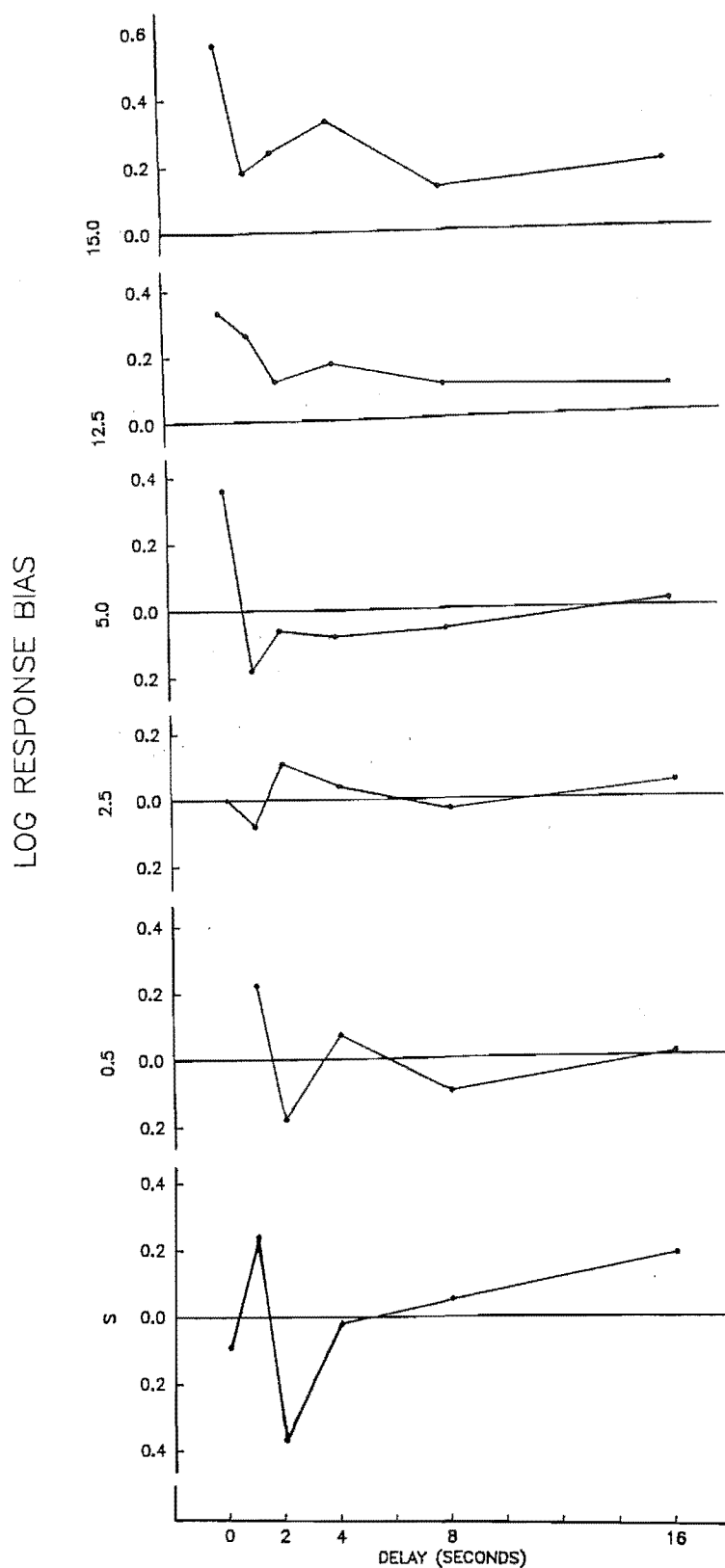


Figure 6. Point estimates of log response bias for the composite saline and drug conditions.

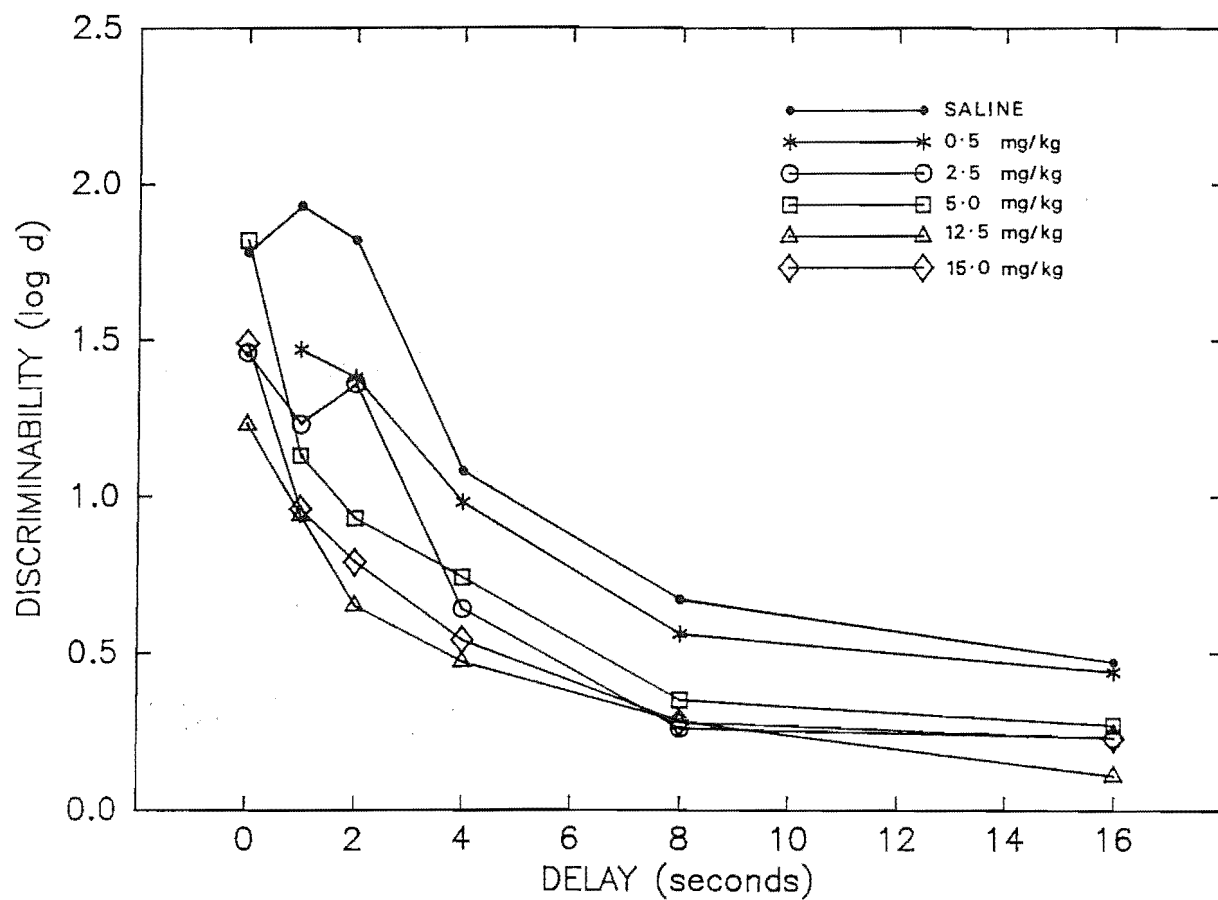


Figure 7. Point estimates of discriminability for the composite saline and drug conditions.

becoming increasingly impaired as the drug dose increased. This was with the exception of the 15 mg/kg dose where performance was less impaired than in the 12.5 mg/kg condition. In addition performance at the 5.0 mg/kg dose level was less impaired than at the 2.5 mg/kg dose level.

In general the discriminability "curves" appear not to diverge, but stay approximately parallel across the drug conditions. Again it was not possible to carry out an analysis of variance on the discriminability data due to missing data values at the short delay intervals. The percent correct data were used for this analysis instead.

Percent Correct. The percentage of trials on which correct matching responses were made was calculated for all the conditions and is presented in Figure 8. The pattern of responding across the delay values and the drug conditions was similar to the pattern for the discriminability values, except that there was less variability in the data. Since the bias was small, log d values and the percent correct values were highly correlated ( $r = .95$ ). A two-way repeated measures analysis of variance was run (Lane, 1981) with the delay interval as one factor and the drug dose level as the other. Both the delay interval  $F(2,7) = 78.5$ ,  $p < .01$  and the drug dose  $F(2,8) = 9.55$ ,  $p < .01$  had a significant effect on the percentage correct.

Figure 9 shows the data collapsed across drug conditions as a function of delay. Percentage correct decreased with increasing delay value, with the difference in performance between the 0 and 8 second delay intervals reaching significance at the 1% level, assessed using Dunnett's test (Keppel, 1973). Figure 10 shows the data collapsed across delays as a function of the drug dose. Percentage correct decreased with increasing drug dose. Compared to the composite saline condition,

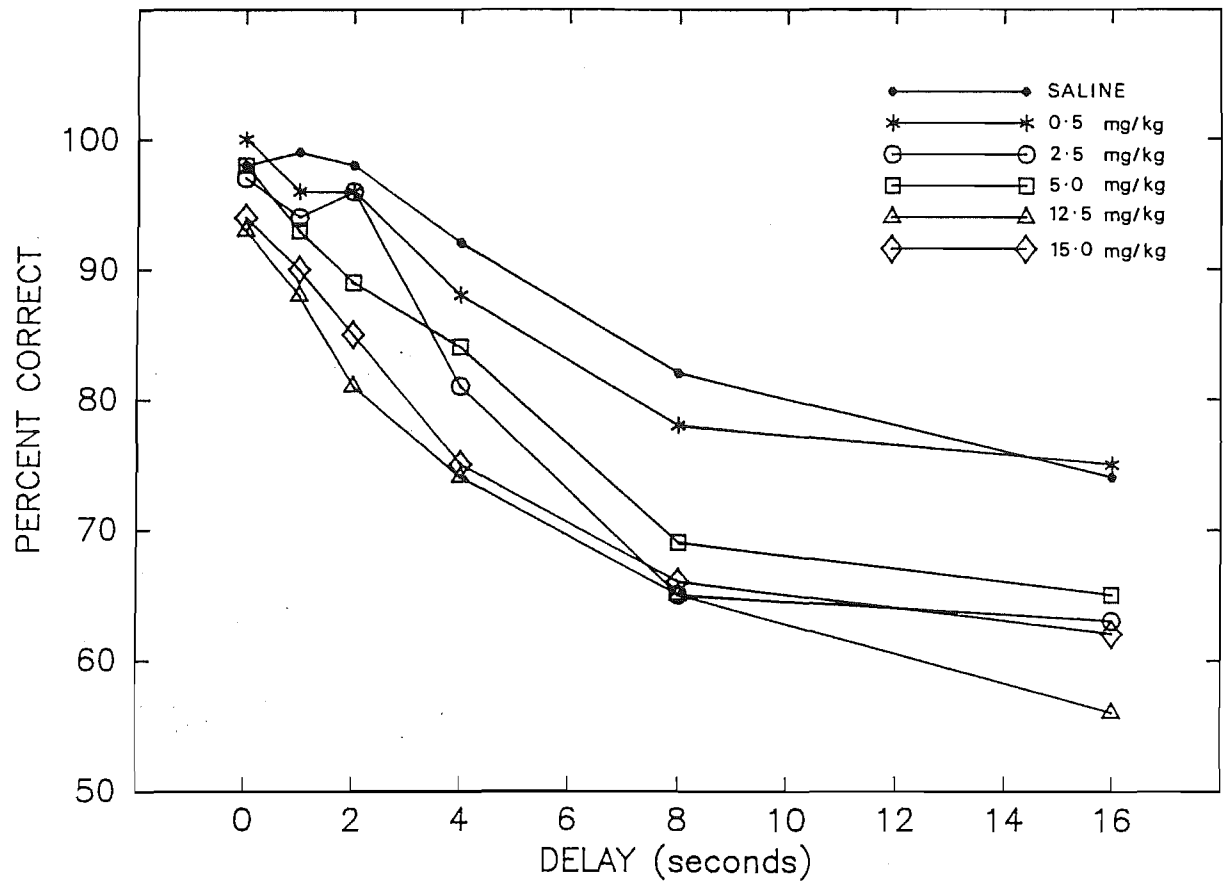


Figure 8. Percent correct for the composite saline and drug conditions.

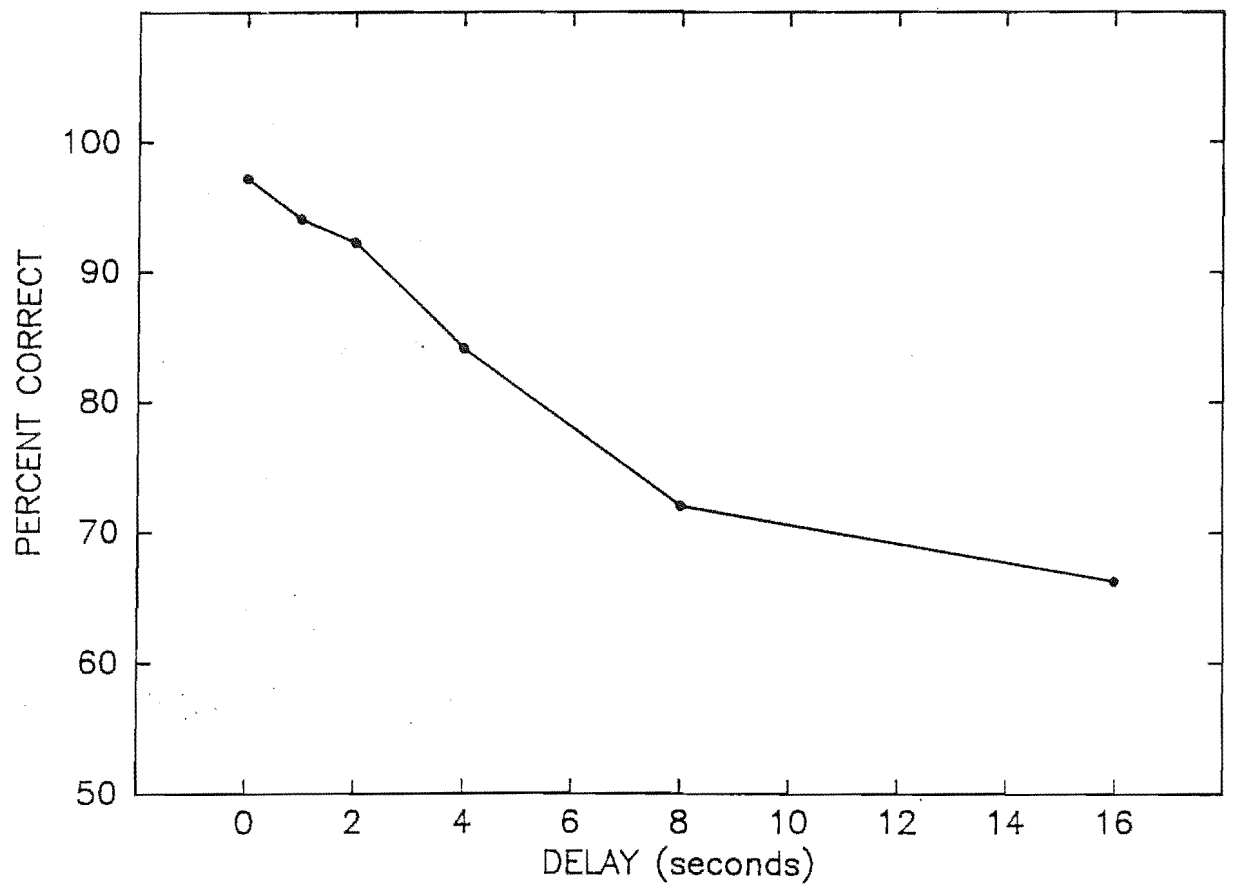


Figure 9. Mean percent correct for the delay intervals.



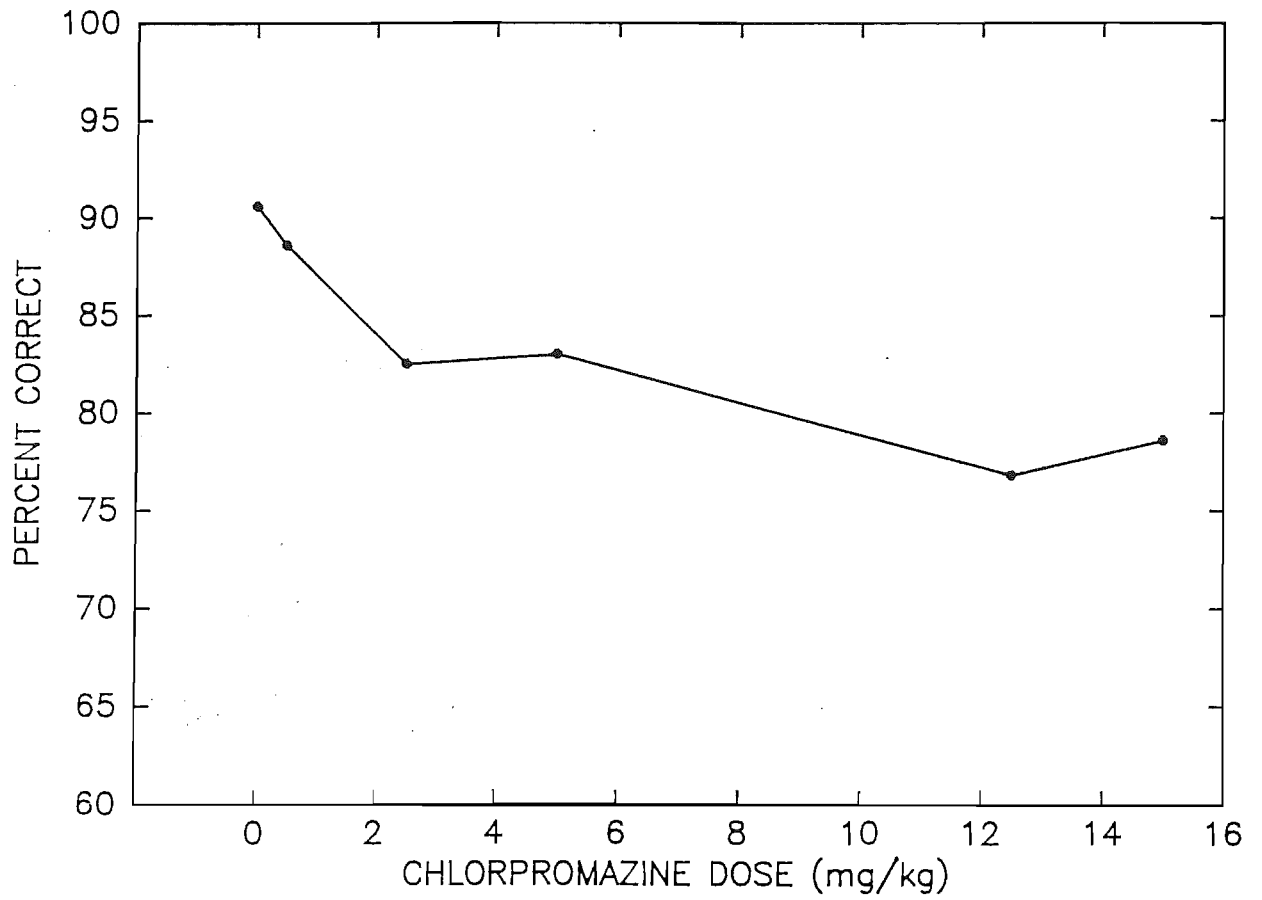


Figure 10. Mean percent correct for the composite saline and drug conditions.

performance showed a significant decrement (1% level) at the 2.5 mg/kg dose level, and all higher doses, using Dunnett's test (Keppel, 1973).

Decay Curve Functions. Both the negative exponential and the rectangular hyperbolic models of decay were fitted to the discriminability data at each drug dose. A summary of the parameters of the best fitting curves obtained is presented in Table 8. Both models provided a good fit to the data which was indicated by the small root mean square (RMS) values. For both the negative exponential and the rectangular hyperbolic models the log d values decreased with increasing drug dose. The b and h values showed little variation from the composite saline level with no systematic increase or decrease with changes in the drug dose.

Figure 11 shows the regression lines for each drug dose. Generally the lines are parallel showing only changes in the initial value and no change in slope across the drug conditions.

Individual Subject Data. To create sufficient data for an analysis of baseline and drug conditions for individual subjects, the data for each subject for all administrations at 0.5, 2.5, 5.0, and 12.5 mg/kg were pooled to form a composite drug condition. These data were compared with that from a 12-day baseline condition. Baseline data were used rather than the saline data as there were insufficient errors in the saline condition to allow the discriminability index to be calculated at short delay values. Even in the baseline data for one subject, there were insufficient errors at the one and two second delays to enable log d values to be calculated. The data from the other four subjects are presented in Figure 12. In all cases the baseline and composite drug condition decay curves are approximately parallel and this was reflected in the parameters of the decay curve

Table 8

Parameters of the Decay Functions for the Composite Saline and Drug Conditions

Dose (mg/kg)	<u>Exponential</u>			<u>Hyperbolic</u>		
	log do	b	RMS	log do	h	RMS
S	2.22	.14	.038	2.68	3.08	.020
0.5	1.63	.11	.016	1.89	4.62	.008
2.5	1.65	.20	.040	2.00	2.21	.051
5.0	1.25	.13	.008	1.49	3.27	.004
12.5	1.04	.18	.005	1.46	1.73	.001
15.0	1.07	.15	.008	1.34	2.65	.017

RMS = Root Mean Square

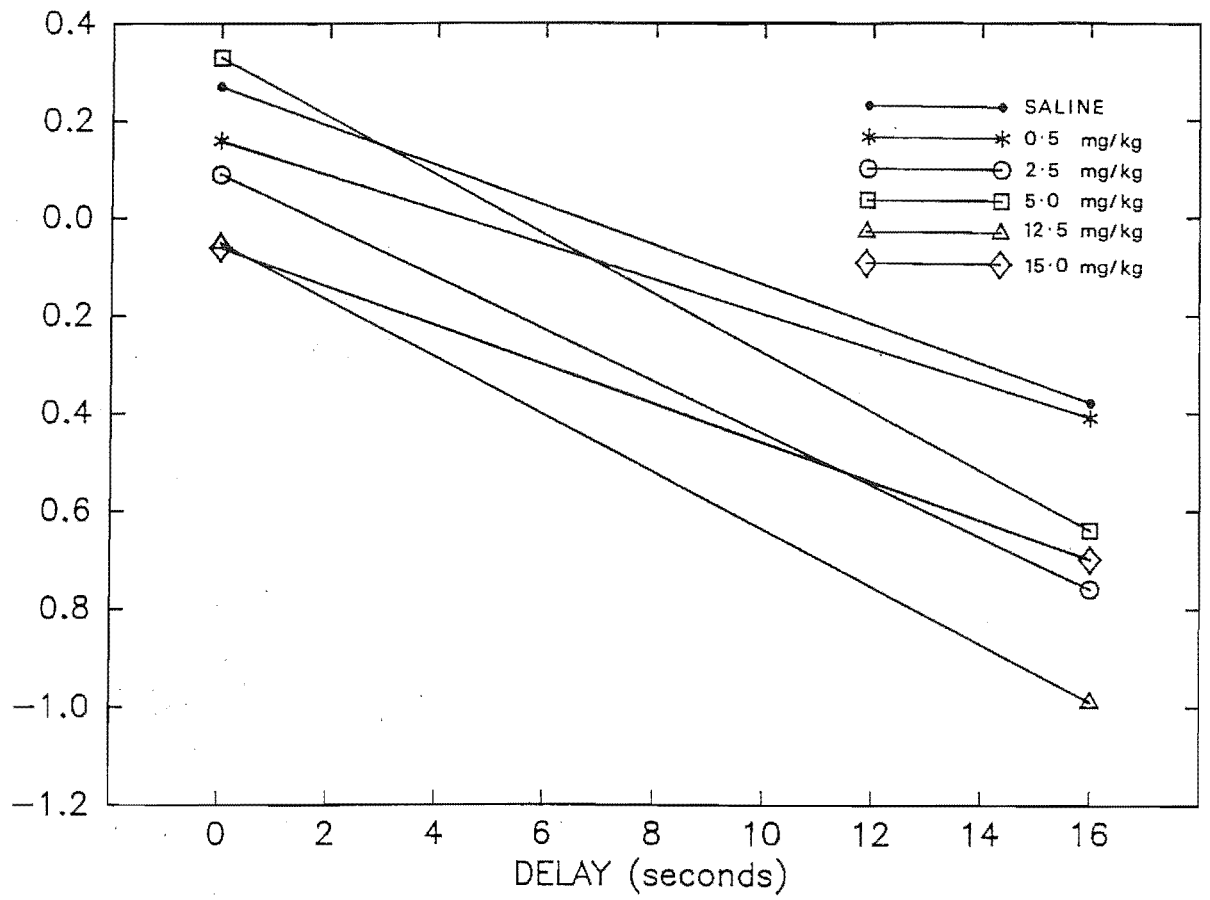


Figure 11. Regression lines for the composite saline and drug conditions.

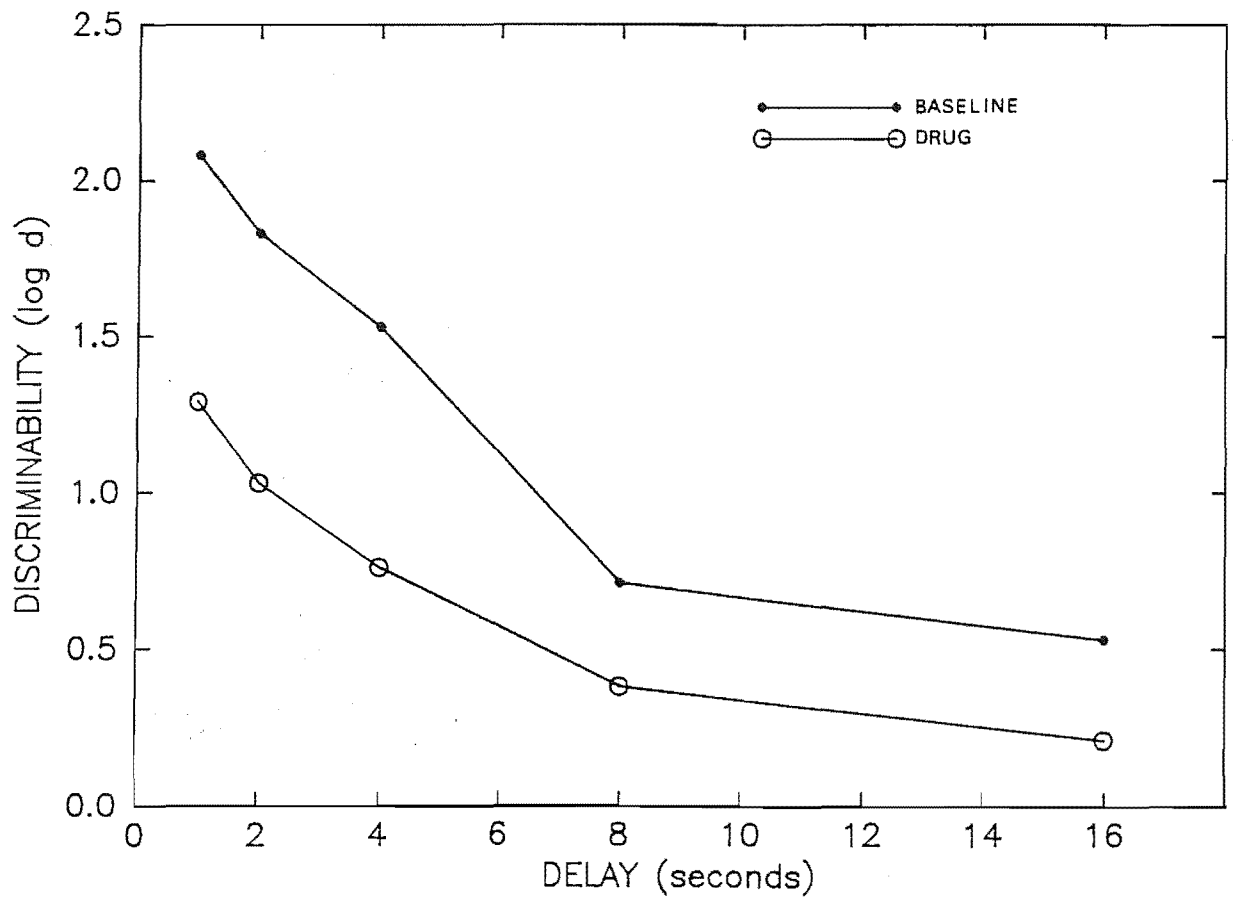


Figure 12a. Point estimates of discriminability for the baseline and composite drug conditions for subject number 1.

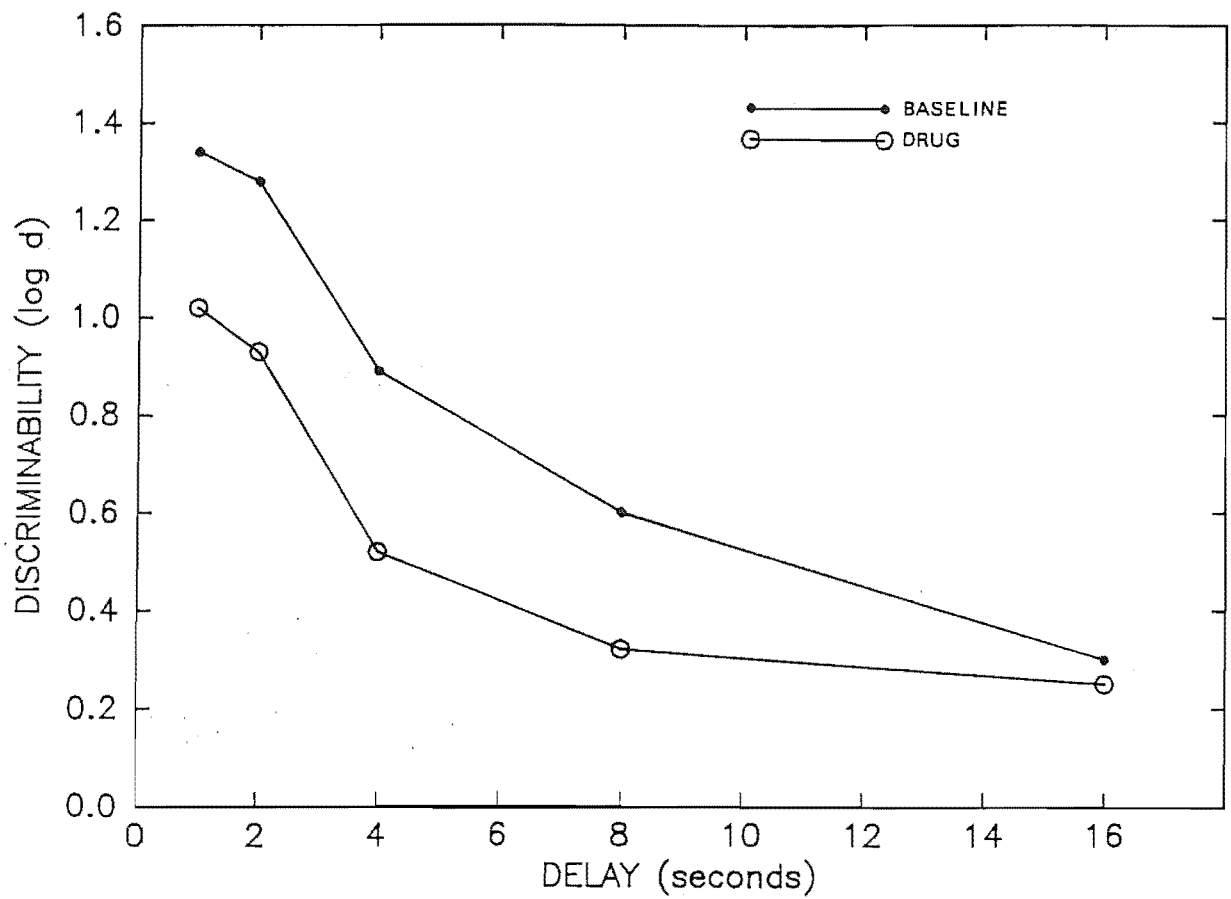


Figure 12b. Point estimates of discriminability for the baseline and composite drug conditions for subject number 3.

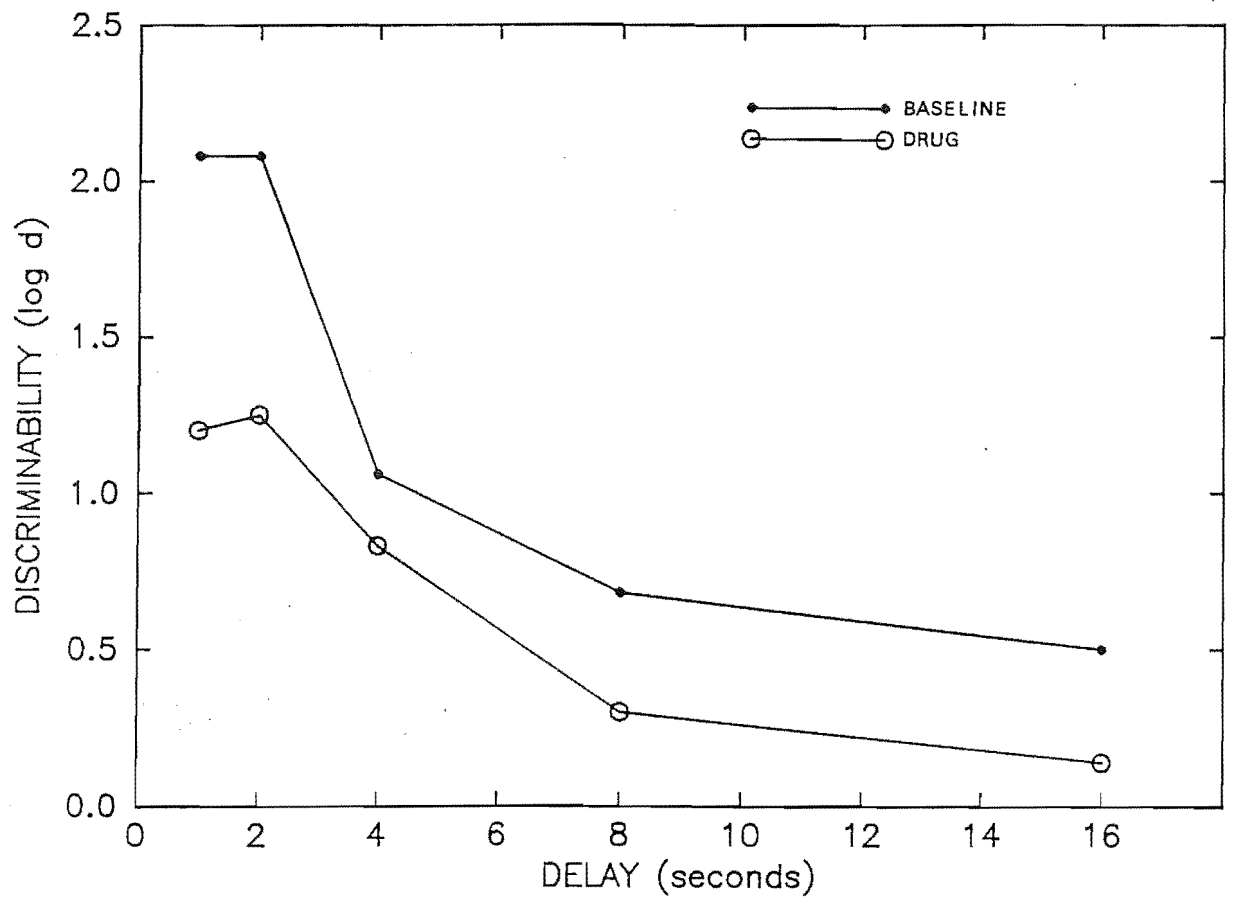


Figure 12c. Point estimates of discriminability for the baseline and composite drug conditions for subject number 4.

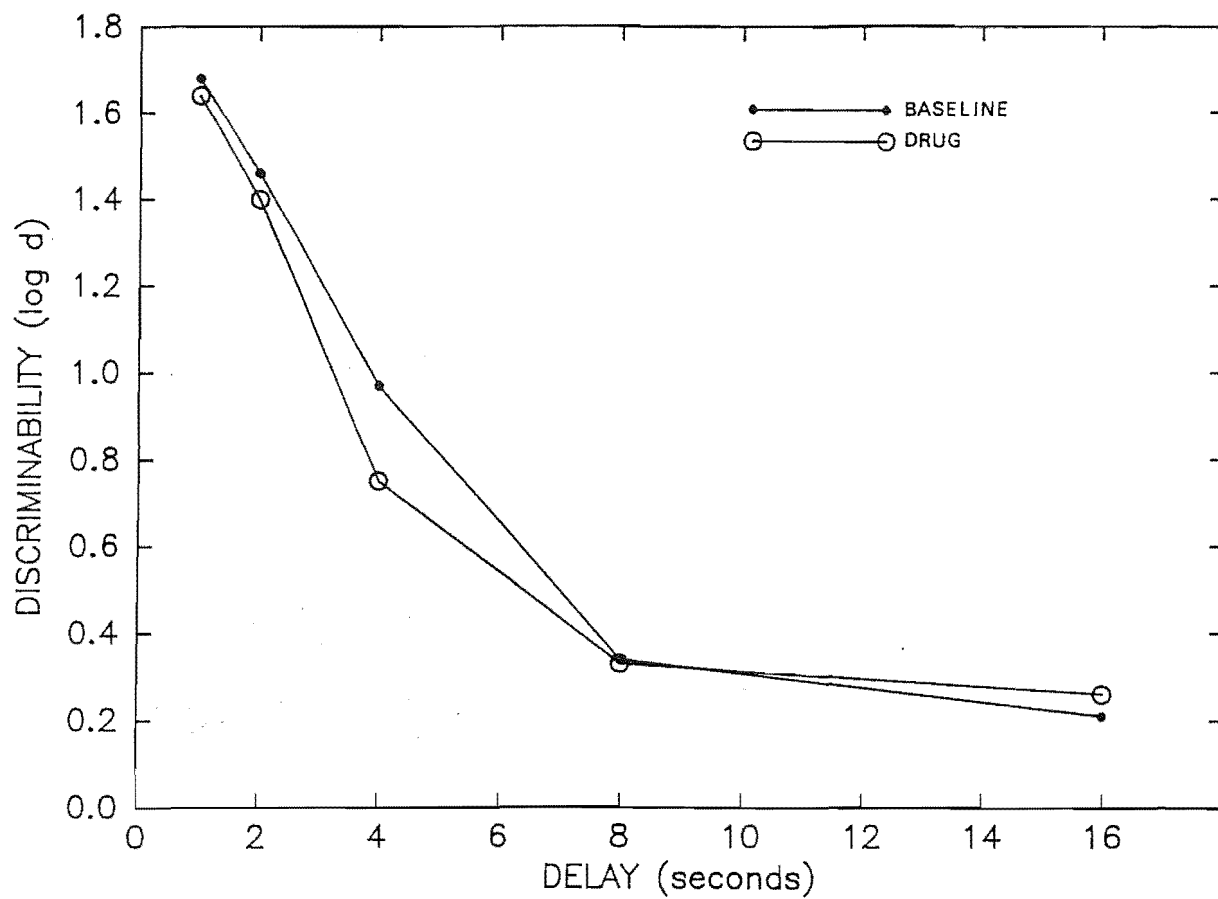


Figure 12d. Point estimates of discriminability for the baseline and composite drug conditions for subject number 5.



functions which are presented in Table 9. The log d values decrease in the composite drug condition relative to baseline but there is no major change in b. It is interesting to note that the drug appeared to have no discernable effect on subject number 5.

#### Non-Parametric Signal Detection Indices

Two other indices of both discriminability and response bias were calculated. These indices are calculated from the hit and false alarm rates rather than the absolute number of responses as the indices in the behavioural model of signal detection are calculated from. The Grier A' Index of discriminability, calculated using equation 3, is presented in Figure 13. The second non-parametric discriminability measure, the sensitivity index, was calculated using equation 6 and is presented in Figure 14. Compared with the log d measure these two indices show less variability, especially at the shorter delays, and there is an obvious ceiling effect which is not apparent in the log d data. There was a greater range of values for the sensitivity index than for the Grier A' measure, and this measure was the more sensitive of the two to changes across the drug conditions. Both the indices showed the same pattern of changes across the delay intervals and dose levels as the log d measure of discriminability.

The Grier index of response bias, B'', calculated using equation 4, is presented in Table 10. The responsivity index of Frey and Colliver (equation 5) is presented in Table 11. These indices show more variability than the log response bias values but the same pattern of changes with drug dose and delay. The Grier B'' index, at high performance levels was very sensitive to small changes in the distribution of hits and false alarms. Small changes resulted in large shifts in the absolute value of B''.

Table 9

Parameters of the Decay Functions for the Individual Subjects

Subject	Condition	<u>Exponential</u>			<u>Hyperbolic</u>		
		log do	b	RMS	log do	h	RMS
No. 1	B	2.33	.12	.025	2.67	4.06	.025
	D	1.46	.16	.004	1.84	2.46	.003
No. 3	B	1.50	.11	.005	1.70	4.64	.007
	D	1.18	.15	.014	1.47	2.61	.006
No. 4	B	2.85	.15	.077	3.03	2.74	.056
	D	1.55	.17	.015	1.82	2.73	.036
No. 5	B	2.09	.20	.009	2.66	1.97	.025
	D	2.07	.22	.019	2.80	1.57	.017

B = Baseline

D = Drug

RMS = Root Mean Square

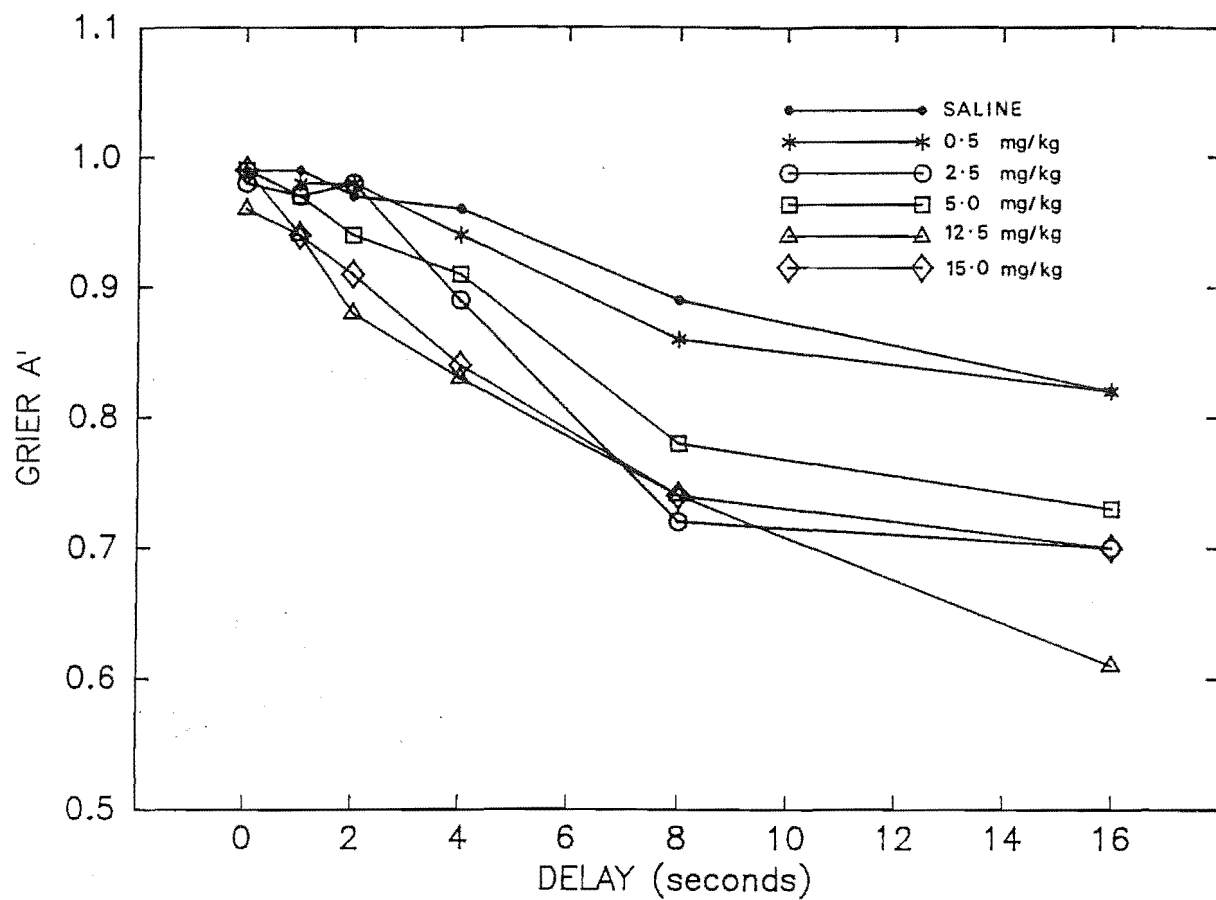


Figure 13. The Grier A' index for the composite saline and drug conditions.

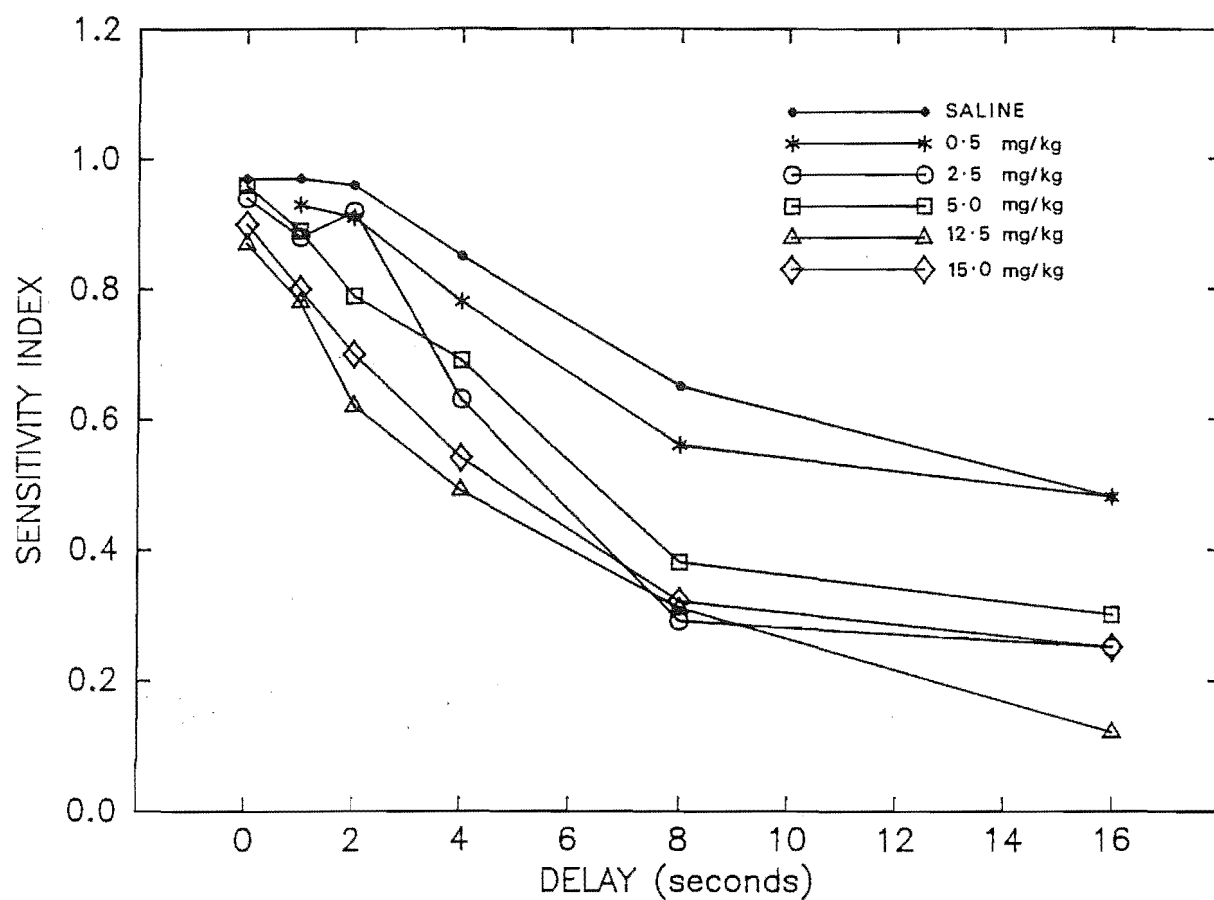


Figure 14. The Sensitivity index for the composite saline and drug conditions.

Table 10

The Grier B" Index Across Composite Saline and Drug  
Conditions for Each Delay Value

Delay	Dose (mg/kg)					
	S	0.5	2.5	5.0	12.5	15.0
0	.33	-	.01	-.49	-.54	-.80
1	-.33	-.42	.16	.64	-.43	-.30
2	.49	.32	-.24	.13	-.16	-.35
4	.06	.01	-.06	.13	-.18	-.38
8	-.07	.13	.02	.05	-.08	-.11
16	-.21	0	-.03	-.01	-.02	-.12

Table 11

The Responsivity Index Across Composite Saline and Drug  
Conditions for Each Delay Value

Delay	Dose (mg/kg)					
	S	0.5	2.5	5.0	12.5	15.0
0	-.17	-	0	.26	.31	.43
1	.17	.22	-.09	-.35	.27	.19
2	-.26	-.17	.13	-.08	.13	.25
4	-.04	0	.05	-.10	.18	.35
8	.05	-.12	-.03	-.07	.12	.17
16	.22	0	.05	.02	.10	.23

### Comparison of Baseline 1 and Baseline 2

To assess the effects of exposure to CPZ, baseline performance prior to exposure to the drug (Baseline 1) and after the drug trials (Baseline 2) was compared. Baseline 2 was formed by pooling data from the last three sessions prior to the beginning of the next experiment. The first of these sessions was an average of five sessions since the end of the drug trials. The value of the discriminability index,  $\log d$ , across each of the delays for the two baselines is presented in Figure 15.

Performance in the second baseline was higher at the shorter delays (1 and 2 seconds) and was at a comparable level in both baselines at the other delay values. There was no significant difference (assessed using the percent correct measure) between performance in the two baselines,  $F(1,4)=1.18$ ,  $p>.05$ . The parameters of the decay functions for the two baselines are presented in Table 12. The value of the estimate of  $\log d_0$ , the initial discriminability was considerably higher in Baseline 2 than in Baseline 1, but there was little change in either the rate of decay,  $b$ , or the half-life,  $h$ .

### Discussion

In the past the majority of studies assessing the effects of drugs on discrimination and memory processes have relied on the visual analysis of the relationship between the performance-by-delay interval curves to determine if there is a drug effect on discrimination and/or retention and memory processes. An effect on retention or memory is apparent by a divergence in the curves which is due to the differential drug effect at longer delay values. There is little standardization in this analysis and problems exist where floor and ceiling effects can also produce divergence in the control and drug

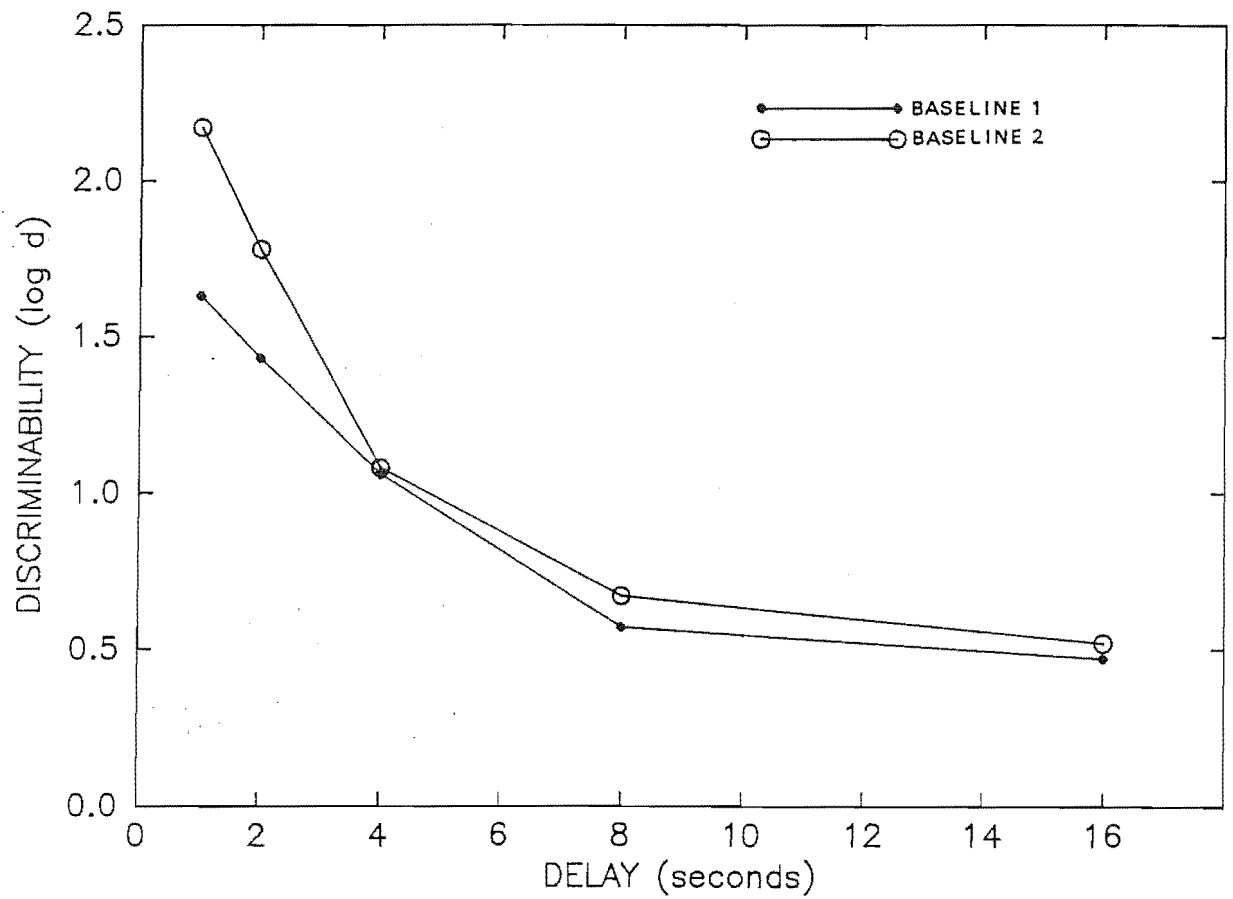


Figure 15. Point estimates of discriminability for Baseline 1 and Baseline 2.



Table 12

Parameters of the Decay Functions for Baseline 1 and  
Baseline 2

Condition	<u>Exponential</u>			<u>Hyperbolic</u>		
	log do	b	RMS	log do	h	RMS
Baseline 1	1.77	.12	.020	2.09	3.85	.007
Baseline 2	2.41	.15	.053	3.11	2.40	.010

RMS = Root Mean Square

accuracy-by-delay curves.

In addition, past studies have generally used percent correct as the measure of performance. Although some studies have used signal detection theory to separate the effects of sensitivity and response bias this has not been done for a delayed detection experiment with drugs. This experiment has shown that the behavioural model of signal detection performance (Davison & Tustin, 1978) can be successfully applied to the analysis of the effects of CPZ. The extension of this model to account for delayed discrimination procedures accounted well for the data obtained using the DMTS procedure.

#### The Effect of Vehicle Control Injections

The first analysis showed the vehicle control injections had no significant effect on variables assessing psychomotor performance. No effect on either centre key latency or side key latency would be expected in the baseline or the saline conditions but an effect due to delay could be postulated. As the delay interval increased the subjects may have moved away from the keys and when the comparison stimuli became illuminated have therefore taken a longer time to respond to them. However, the analysis showed there was no effect due to the increasing delay.

In the baseline and saline conditions there was no decrement in performance as a function of the saline injections, but across all conditions there was the expected decrement in performance as the delay interval increased. Performance assessed using the percent correct and point estimate of discriminability,  $\log d$ , showed that matching accuracy remained high until the two second delay interval. Performance decreased considerably at the 4, 8, and 16 second delay intervals. Performance at the shorter delays was at a maximum for several of the conditions and this ceiling effect was seen most

clearly in the percent correct data. With the discriminability data, the effect was not so apparent. In this case, there were insufficient errors to calculate a log d value until the one second delay interval for baseline and the two second delay interval for the saline conditions. The maximum log d value obtained depends on the number of trials which are distributed in the signal detection matrix. In this case the maximum number of trials was 300, and when there was just one miss and false alarm the log d value was 2.17. This value was attained at the two second delay interval for the S2.5 mg/kg condition.

Performance decreased as the delay interval increased but was still well above chance level at the 16 second delay interval. Performance at the 16 second delay interval reached a minimum of 66% in the S2.5 mg/kg condition. Above chance performance was also indicated by the log d values which remained above 0 at the longer delays. Had performance been at chance level there would have been approximately equal numbers of entries in all cells of the signal detection matrix and the value for the point estimate of log d would have approached 0.

The controlled reinforcement rate procedure meant the subject had to avoid continually choosing either one comparison stimulus colour or one position (left or right), in order to collect the maximum number of reinforcers which were available. The procedure forces the subject to abandon colour or position biases, so they are theoretically choosing the comparison stimulus on the basis of their "memory" of the sample stimulus. When errors are distributed approximately equally between misses and false alarms, the point estimate of bias approaches zero. As more errors occur in one of the error cells the bias value increases correspondingly. In the baseline and saline conditions the point estimates of bias were small, in the range of  $-.30$  to  $+.30$ , across the delay values. The subjects as a group appeared to have an

inherent bias to respond to the red comparison stimulus as the majority of the bias values were positive. This occurred even though the bias values were small and this may reflect a preference of the pigeon for red over green.

Since bias in the subjects responding was negligible, the percent correct measure was providing a reasonably "uncontaminated" estimate of discriminability. This is also evident in the high correlation between percent correct and log d. Therefore it was appropriate to use the percent correct data in the analysis of variance, since missing data points meant the analysis could not be carried out using the point estimates of discriminability. The analysis confirmed that the vehicle control injections of saline were having no significant effect on matching performance. This means that the procedure of injecting the subjects did not affect the subjects performance and effects when CPZ was administered could be attributed directly to drug effects and not to procedural variables.

It is interesting to note that performance was in fact higher, in the majority of cases, in the saline conditions than in the baseline condition across the delay values. While this increase was not significant, it did suggest that there was a drift in performance. (This finding will be discussed later). For this reason, a composite saline condition was formed from three days on which saline was administered which were taken at random.

The percent correct and log d values for this composite saline condition were close to the mean of those for the saline conditions and slightly higher than those for the baseline condition. In this composite saline condition the log d values at the 1 and 2 second delay intervals were higher than at the 0 second delay interval. This paradoxical finding can be explained by the FR5 response requirement on the sample stimulus. Since the subjects could not count very well

they would peck the sample stimulus with more than the required number of pecks. In the zero second delay condition, the sample stimulus would have extinguished and the comparison stimuli become illuminated before the pigeon ceases pecking. This "extra pecking" would in effect equate the tasks at the short delay intervals. It should also be noted that performance at the short delay values was very high and a difference of a few errors can distort the log d values, more so than the percent correct values.

#### The Effects of Chlorpromazine

Five doses of CPZ were tested. The lowest four doses: 0.5, 2.5, 5.0, and 12.5 mg/kg were tested in a randomized design across the single subjects. Each subject received three administrations of each of the four doses. This series of drug trial was followed by three administration of a higher dose, 15 mg/kg. Only the data from the initial drug trial were included in any analysis of variance.

At the higher doses CPZ appeared to be having a psychomotor effect on some subjects. This was apparent in response failure by two subjects at the 15 mg/kg dose level with one subject completing only 12 of the 300 available trials. The centre key latency and side key latency measures showed no significant increase as the dose increased but the means were generally larger at the higher doses. It is interesting to note that the mean centre key latency and side key latency were less for the 15 mg/kg condition than the 12.5 mg/kg condition which was an unexpected result. Generally though, these increases in the centre key latency and side key latency measures are consistent with the sedative effects of CPZ.

Bias, as assessed using the point estimate of bias from the behavioural model of signal detection was again kept to a minimum by the controlled reinforcement rate procedure. At short delay values

across the drug conditions, there was often wide fluctuation between positive and negative bias values and at the 15.0 mg/kg level the bias value approached +0.6 at the 0 delay interval. These findings, and the relatively higher bias values at shorter delay intervals, can be accounted for by high performance at short delays. This means that a difference of 4 or 5 in the distribution of errors between the false alarm and miss cells of the signal detection matrix will result in a higher bias score than when the overall performance is higher. In this case the low overall bias in the data meant that once again the percent correct measure of performance and log d were highly correlated.

Across the drug conditions matching performance showed the expected decrement as a function of the delay value, when measured using both percent correct and log d. In contrast to performance in the saline conditions, in the drug conditions performance was not subject to a ceiling effect. Performance at the 0 second delay interval was 100% for the 0.5 mg/kg condition, otherwise performance at all delays and all doses was below 100%. Performance at all doses decremented with increasing delay, but even at the higher drug doses, performance remained above the chance level of 50% correct or a log d value of 0. Therefore there were no floor effects in the data.

Performance also showed a significant decrement as a function of the dose of CPZ. Generally as the dose increased, performance decreased with two exceptions. First at several delay values, performance at the 5.0 mg/kg dose level was higher than at the 2.5 mg/kg dose level. For example, at the 0 delay interval the log d value for the 5.0 mg/kg condition was 1.82, and for the 2.5 mg/kg condition it was 1.46. While this may be suggestive of a U-shaped dose-response function, given that performance decreased at the higher doses, it could also indicate an error in the preparation of the drug solutions,

as simple as the mis-labelling of the solutions. The second exception is performance at the 15.0 mg/kg dose level which was equal or greater than performance at the 12.5 mg/kg level across the delay values. Again while this is initially suggestive of a U-shaped dose response function, another probable explanation exists. The injections at the 15.0 mg/kg dose level were given in a block at the conclusion of the randomized trial of the four lower drug doses. Exposure to these doses may have resulted in the development of tolerance. This would mean the subsequent exposure to the higher drug dose would not result in the same degree of impairment as would have been the case had the same dose level been administered to drug-naive subjects. This interpretation is supported by the finding that performance was higher in the saline conditions than in the baseline condition. Since the saline injections were administered throughout the drug trial, performance in the sessions intervening between drug injections may have shown improved performance due to the subjects improving on the task as a result of exposure to the drugs.

Both the percent correct and the discriminability ( $\log d$ ) data show the performance-by-delay interval "curves" were approximately parallel with no marked convergence or divergence. This suggests that the drug was having no specific effect on retention or memory processes. The application of delayed detection models derived from the behavioural model of signal detection was used to quantify changes in performance with drug administration. Both the negative exponential and the rectangular hyperbolic models of decay were fitted to the discriminability data across the delay values. In all cases the functions provided a close fit to the data as shown by the small value of the root mean square (RMS). For both the functions, the value of the initial discriminability,  $\log d_0$ , decreased as a function of drug dose with the two exceptions already noted (higher performance at the

5.0 mg/kg dose than at the 2.5 mg/kg dose, and at 15.0 mg/kg dose compared to the 12.5 mg/kg dose).

The rate of decay,  $b$ , and the half-life,  $h$ , are similar to the value obtained in the composite saline condition across all the drug conditions. The mean of  $b$  and  $h$  across the drug conditions ( $b = .15$  and  $h = 2.90$ ) is very close to the composite saline values ( $b = .14$ ,  $h = 3.08$ ). In addition there was no increasing or decreasing trend in the values for  $b$  or  $h$  as the dose increased.

This analysis shows CPZ was affecting only the value of  $\log d_0$ , the initial discriminability and not the rate at which discriminability was changing as a function of time, assessed by either the rate of decay,  $b$  or the half-life,  $h$ . This means there was no differential effect caused by the drug as the delay increased. Had there been a differential effect, it is likely a significant interaction effect between dose and delay in the analysis of variance would have occurred. The lack of an interaction is also shown by the virtually parallel regression lines for the drug doses. Since the slope of the lines is approximately equal, it means there is no differential rates of decay as a function of the increasing delay value. In terms of basic behavioural processes assessed by the task, CPZ was affecting discrimination processes but not retention or memory processes.

This conclusion is supported by the analysis of the data from individual subjects for the composite drug condition. To compare baseline and drug performance from the individual subjects the data from all 12 administrations of doses 0.5-12.5 mg/kg were pooled. Analysis of this composite drug condition showed that for subjects 1, 3, and 4 the performance-by-delay interval curves for the baseline and composite drug condition were approximately parallel. The curves showed a difference only in the level of performance at short delays.



This was confirmed by the analysis of the decay functions. For subjects 1, 3, and 4 the log d estimate for both the negative exponential and the rectangular hyperbolic models of decay was less in the composite drug condition than in the baseline condition. For the same subjects, the values for b and h are comparable across the two conditions.

For subject number 5 the drug appears to have had a negligible effect, apart from a 4% decrease at the 4 second delay interval. This suggested that pigeons may differ markedly in their susceptibility to CPZ and points to the need for single subject design experiments in this type of research. Had there been another "non-responder" subject in the group it may have caused the drug effects to be masked when the group data was pooled. Since the analysis of the effects of CPZ was carried out including the data from subject number 5, the differences that were found are conservative. Had the data from subject number 5 been removed from the analysis the differences between the composite saline and the drug conditions would have been even more apparent.

#### Non-Parametric Indices

Two non-parametric indices of discriminability, the Grier A' index and Frey and Collivers sensitivity index were compared to the discriminability index derived from the behavioural model of signal detection. Because of the nature of the formulae, where both non-parametric indices are calculated using the probability of a hit and the probability of a false alarm, the indices can vary between a maximum value of one and a minimum value of zero. At high performance levels at short delays, this meant there was a strong ceiling effect in the data, especially for the Grier A' index. Since the log d measure is calculated using the number of responses in each cell of the signal detection matrix, the maximum value is determined by the

total number of entries in the matrix. Therefore in situations where the overall level of performance is high, but where subtle changes are occurring, the log d index may provide a better measure of discriminability.

The non-parametric indices of response bias, Grier B" and the responsivity index (Frey and Colliver, 1973), showed the same pattern of changes across the delay intervals and dose levels as the response bias index from the behavioural model of signal detection. For both indices there was more variability than the log response bias measure. Given the problems with the B" index, this needs to be interpreted with caution. All the bias indices however, were kept to a minimum by the controlled reinforcement rate procedure.

#### Global Drug Effects

Exposure to CPZ appears to have had both an acute effect at the time of administration and a more global effect on the subjects performance. As previously mentioned there was a drift in performance apparent both in the analysis of the saline conditions and the 15 mg/kg dose level. Therefore a comparison between performance prior to drug administration, Baseline 1, and after the administration of CPZ, Baseline 2, was carried out. Although a second baseline was not part of the procedure as originally planned, for each subject there were sufficient sessions following washout from the last drug injection before the beginning of Experiment 2 to enable Baseline 2 to be formed. Exposure to CPZ increased performance at the shorter delays, while performance was comparable at the 4, 8, and 16 second delay values. Although these differences were non-significant the decay function parameters showed marked differences between the two baselines. For both the negative exponential and rectangular hyperbolic decay models, the estimate of log do was higher in Baseline

2 than in Baseline 1. This occurred while there was no appreciable change in either the rate of decay,  $b$ , or the half-life,  $h$ . This suggests that exposure to CPZ increased the ability of the subjects to discriminate in Baseline 2, while having no effect on memory or retention processes.

#### A Model of Chlorpromazine Action

The results of this experiment strongly suggest the CPZ is having quite a specific effect on the basic behavioural processes involved in the pigeon's performance of the DMTS task. Both the group data and that from the individual subjects showed that CPZ produced a dose-dependent decrease in the initial discriminability as assessed by log  $do$  in the negative exponential and rectangular hyperbolic decay functions. This decrease in performance occurred at doses that had no effects on the variables of psychomotor performance assessed in this experiment. Therefore at doses where there is no sedative effect, the subjects cognitive functioning was significantly impaired. Using the model proposed by Heise and Milar (1984), where no-delay performance assesses just discrimination processes, zero-delay performance assesses encoding and retrieval processes in addition to discrimination processes, and  $x$ -delay performance assess retention or memory, the results show that CPZ was affecting the subjects discrimination and/or encoding and retrieval processes. The drug had no effect on the rate at which the discriminability declined as a function of the delay interval. Therefore the drug had no specific effect on retention or memory processes.

The results of this experiment are similar to the findings from previous research. CPZ has been found to cause a dose-dependent decrease in performance using no-delay procedures, but that a relatively high dose is needed to result in significant impairment

(see Chapter Two). Experiments using zero-delay procedures have also found CPZ causes a dose-dependent decrease in performance. Whether this is due to the effects the drug has on discrimination processes and/or encoding and retrieval processes has not been determined. Past research on the effects of CPZ on delayed discrimination shows there is no differential effect as the delay interval increases. Performance at longer delays is determined by the baseline level of responding and not specifically by the drug dose.

This finding may not be specific to the effects of CPZ. Heise and Milar (1984) in a comprehensive review of drugs and stimulus control conclude that much past research that has concluded that drugs affect memory or retention, may be erroneous due to a failure to examine the effects of different levels of control by pre-delay stimuli. They comment "thus flattening of the short duration end of the control accuracy-by-interval curve due to ceiling effects might have been responsible for the occurrence of nonparallel drug and control accuracy-by-interval curves" (p. 162). Heise and Milar note that when the nondrug levels of stimulus control were lower drug effects on retention have not generally been observed.

Such effects have been found using delayed response alternation procedures in which the ITI is varied systematically (Heise, 1975). Heise, Connor, and Martin (1976) using rats as subjects, found scopolamine impaired discrimination but did not affect retention; the drug reduced alternation accuracy by approximately the same amount at each of the five delay values tested. The effects of d-amphetamine were quantitatively similar. When the delayed comparison procedure, DMTS, was used with monkeys as subjects, a similar pattern of results was found for both scopolamine (Glick & Jarvik, 1970), and d-amphetamine (Glick & Jarvik, 1969).

A series of experiments using paired delayed comparison

procedures has shown that various drugs decrease zero-delay performance but do not affect retention in pigeons. Such results were found for sodium amobarbital (Hulme, Sahgal, & Iversen, 1979; Sahgal, Hulme, & Iversen, 1980a), ethanol (Sahgal, Eckberg, Howell, & Iversen, 1980b) and chlordiazepoxide (Sahgal & Iversen, 1978). (However, a later study by Sahgal and Iversen (1980), using high doses of chlordiazepoxide found no impairment in either zero or x-delay performance). These conclusions are supported by the findings that doses of the drugs that affected zero-delay discrimination did not alter the no-delay simultaneous discriminations. In addition, the similarity between the slopes of the control and drug retention curves was not due to the fact that the level of stimulus control at zero-delay was lower under drug conditions than under control conditions.

In the case of CPZ, while there is clear evidence that it causes no specific effect on memory or retention processes, neither the present experiment nor previous research allows a definitive conclusion concerning the action of CPZ on discrimination, encoding, and retrieval processes. It would be relatively easy to determine the locus of drug action using the MTS procedure. If performance was affected at zero-delay at a dose that did not affect no delay performance then at that dose CPZ would not be affecting discrimination processes. At higher doses however, discrimination processes may also be affected as shown by previous research using no-delay procedures.

For the present purposes no distinction will be attempted between CPZ's effects on discrimination and/or encoding and retrieval processes. The concern will be with the model of CPZ action that distinguishes these effects from effects on memory and retention processes. The next two chapters in this thesis describe experiments that seek to validate the proposed model of CPZ action. The first

experiment aims to mimic the effects of CPZ using a change in the DMTS procedure and the second aims to compensate for the drug effect again using a procedural variation.

## CHAPTER FIVE

### Investigation of the Model of Chlorpromazine Action

#### Experiment 2

If, as was argued in Chapter Four, the major effect of CPZ on performance in DMTS is a specific effect on discrimination and/or encoding and retrieval processes, it should be possible to mimic the effects of CPZ action by a procedural manipulation that also affects these processes. The main features of the DMTS procedure are the sample-stimulus parameters, the delay interval conditions and the ITI conditions. Since the discrimination, encoding, and retrieval processes are activated at the start of the trial it is likely that procedural variations in the sample stimulus parameters should also affect these processes.

As mentioned in Chapter One, various stimulus characteristics have a direct effect on the level of matching performance. Accuracy of DMTS performance is influenced by the number of stimuli used in the sample set, the presentation time of the sample stimuli, the number of responses required to the sample stimulus, and when differential response patterns are required to the sample stimuli. As the discrimination becomes more "difficult" performance decrements: eg, when there are more stimuli in the sample set, when samples are presented for a short time only, and where there is a low response requirement on the same stimulus. In general, percent correct was used as the measure of performance in these studies. Not only does this mean that discriminability may be confounded with effects on bias, but the analyses does not indicate whether the procedural variations are affecting the initial discriminability or the rate at

which discriminability decrements.

There is some experimental evidence that procedural variations in stimulus characteristics affect DMTS performance in the same way that CPZ does, i.e., via a change in the initial discriminability. This evidence comes from analyses of data using the behavioural model of signal detection. McCarthy and White (in press) reanalyzed data, using the log (correct/error) ratio, from an experiment where the sample stimulus requirement was changed. Data from a DMTS experiment by Roberts (1972), where the response requirement for the sample stimulus was a FR1, FR5, or FR15 schedule, was reanalyzed. The delay intervals between the sample stimuli being extinguished and the comparison stimuli being illuminated were 0, 1, 3, or 6 seconds. The log C/E ratio was plotted as a function of the delay for each sample stimulus response requirement. Both the negative exponential and the rectangular hyperbolic decay functions were fit to the data. For both models, the log do estimate increased as the response requirement increased. Correspondingly as the estimate of the initial discriminability increased, estimates of the rate of decay,  $b$ , decreased and the half-life,  $h$ , increased. While McCarthy and White conclude that this result is consistent with findings from human short-term memory studies, where rehearsal raises the level of the short-term retention curve and decreases the rate at which the curve falls, other studies suggest that the effects of altering aspects of the sample stimulus are limited to changes in the initial discriminability, log do.

White (1985) reanalyzed data from two studies where the duration of the sample stimulus was varied. In the first study by Nelson and Wasserman (1978), the sample duration was varied across four delay intervals in a successive matching-to-sample procedure. The log ratio of the matching to nonmatching responses was used as the measure of



performance. As the sample duration increased from 3 to 12 seconds, log do increased from 0.33 to 0.80 with no systematic change in the value of b. In the second study by Grant (1976), where a DMTS procedure was used, again the log do values increased as the stimulus duration increased from 1 to 14 seconds. The b values did not change across the conditions with values in the range of 0.04-0.06.

The effects of another sample stimulus characteristic, the number of presentations of the stimuli, has also been investigated using the negative exponential model. White (1985) reanalyzed data from an experiment by Grant (1981), where the sample stimulus was presented either 1, 2, or 3 times at the beginning of the trial. It was found that the log do values increased as the number of repetitions increased, but there were no changes in the value of the rate of decay, b.

In summary, three studies assessing the effects of changing either the duration or the number of repetitions of the sample stimulus show that such manipulations affect only the value of the initial discriminability, log do. The study by Roberts (1972) suggests that altering the response requirement on the sample stimulus may alter both the initial discriminability and the rate of decay. White (1985) also investigated changing the response requirement on the sample stimulus. At an FR1 requirement the log do value was 0.77 and the b value was 0.11. At an FR5 requirement the values were 1.53 and 0.12 respectively. The results of this study cast doubt on the findings of Roberts (1972) and strongly suggested that changes in any aspect of the sample stimulus will result in a change in the initial discriminability of the sample, with no changes in the rate at which discriminability decrements. This conclusion is supported by the results of an experiment carried out by White (1985) where increasing the wavelength difference between the sample stimuli increased the

initial discriminability,  $\log d_0$ , but did not affect the rate at which discriminability,  $b$ , changed.

The aim of the present experiment was to further validate the model of CPZ action by systematically changing the response requirement on the sample stimulus. If, as previous research strongly suggests, this results in a change in  $\log d_0$  but not in the estimates of either the rate of decay,  $b$ , or the half-life,  $h$ , the results should mimic those obtained with CPZ. In addition, the experiment provided additional data on the role of sample stimulus requirements in the DMTS procedure.

## Method

### Subjects

The same five subjects were used as in Experiment 1.

### Apparatus

The same apparatus was used as for Experiment 1.

### Procedure

At the beginning of the experiment the subjects were working on an FR5 response requirement on the sample stimulus, having completed Experiment 1. In Experiment 2, all the procedural variables remained identical to those Experiment 1 except for variations in the response requirement on the sample stimulus. The response requirement was systematically decreased by 1 response i.e., FR5, FR4, FR3, FR2, and FR1 during the experiment. The subjects performed at each response requirement until a stability criterion was reached as in Experiment 1 (Harnett et al., 1984). Data from the final three sessions in each response requirement condition were pooled across the five subjects,

with data from Baseline 2 (see Experiment 1) used as the FR5 condition data. A third baseline was run at the conclusion of the response requirement manipulations, where the subjects worked on the standard FR5 procedure.

## Results

The number of responses to red and green comparison stimuli following red and green sample stimuli for each of the response requirement conditions is presented in Table 13. The total number of trials at each delay for each condition was 300.

### Bias

Values for the point estimates of bias for each delay value and each condition are presented in Table 14. Due to insufficient entries in the error cells at zero delay for all but the FR1 condition, bias values could not be calculated. The bias values were small, ranging from  $-.16$  to  $.31$  with 76% of the values being positive, indicating a consistent, but negligible, bias toward responding to the red comparison stimulus. Four of the five instances of a negative bias value occurred in the FR1 condition, with the other instance in the FR2 condition.

### Discriminability

Point estimates of discriminability for each condition and each delay value are presented in Figure 16. Only once was the maximum log d value reached at the 1 second delay interval in the FR5 condition. The lowest log d value reached was  $0.24$  at the 16 second delay interval in the FR1 condition. Across all the conditions, performance decreased as the delay interval increased. In the FR2 condition the

Table 13

Number of Red and Green Comparison Key Responses  
Following Red and Green Sample Stimuli for the  
the Sample Stimulus Conditions

Response Requirement	Delay	C. R. GG	F. A. GR	Miss RG	Hit RR
FR5	0	150	0	0	150
	1	149	1	1	149
	2	147	3	2	148
	4	137	13	10	140
	8	119	31	22	128
	16	114	36	33	117
FR4	0	150	0	2	148
	1	147	3	1	149
	2	148	2	2	148
	4	136	14	6	142
	8	113	37	30	120
	16	101	49	41	109
FR3	0	150	0	0	150
	1	146	4	1	149
	2	148	2	1	149
	4	131	19	14	136
	8	102	48	24	126
	16	84	66	32	118
FR2	0	150	0	4	146
	1	145	5	9	141
	2	147	3	3	147
	4	126	24	7	143
	8	116	34	30	120
	16	90	60	44	106
FR1	0	147	3	4	146
	1	146	4	8	142
	2	137	13	11	139
	4	130	20	24	126
	8	109	41	37	113
	16	107	43	67	83

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C. R. = Correct Rejection

F. A. = False Alarm

Table 14

Point Estimates of Log Response Bias Across Sample  
Stimulus Conditions for Each Delay Interval

Delay	FR Value				
	5	4	3	2	1
0	-	-	-	-	-.06
1	0	.24	.31	-.13	-.16
2	.09	0	.15	0	.04
4	.06	.20	.07	.30	-.05
8	.09	.06	.20	.03	.03
16	.02	.06	.23	.10	-.15

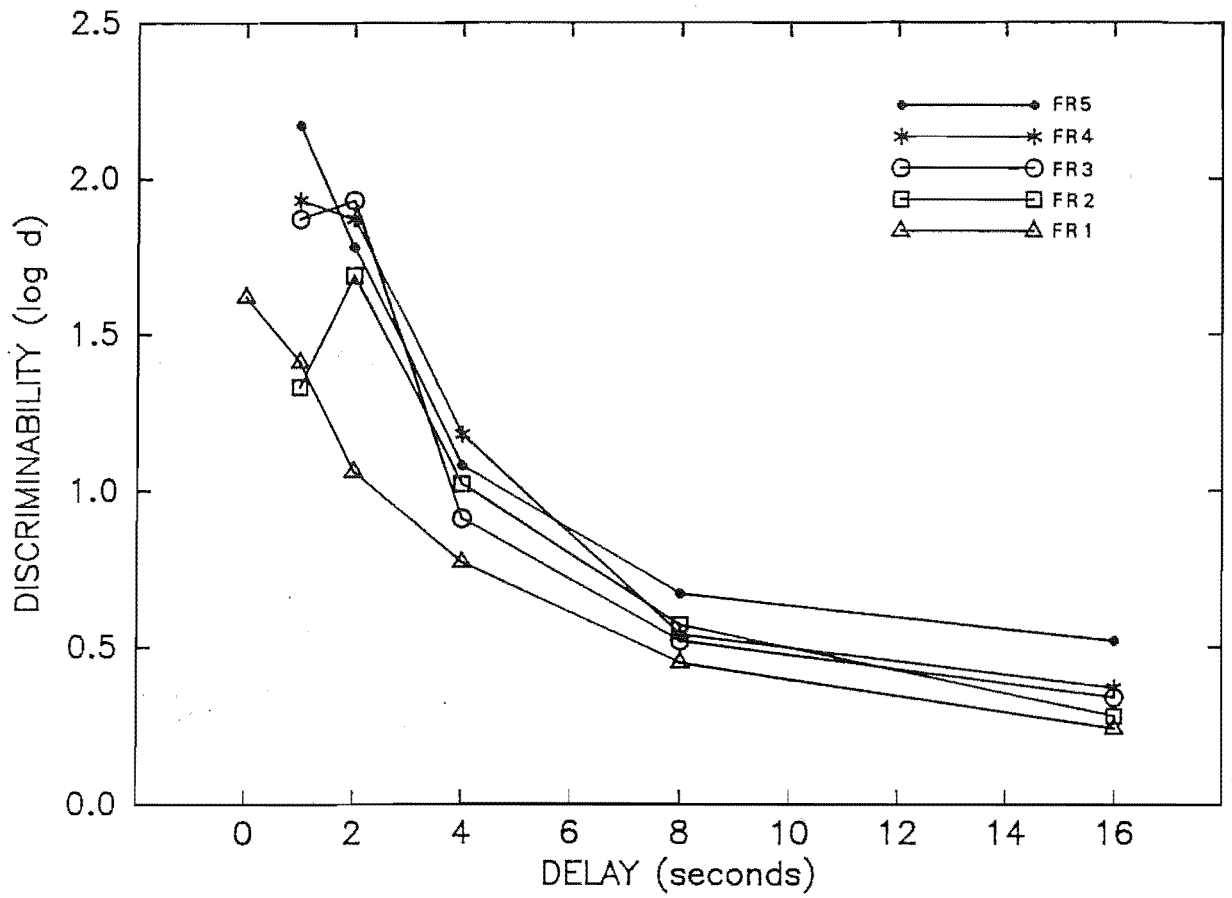


Figure 16. Point estimates of discriminability for the sample stimulus conditions.

decrease was not as orderly as in the other conditions probably due to uncharacteristically low performance at the 1 second delay condition. Performance also decreased as a function of the response requirement, with generally the highest performance in the FR5 condition and the lowest in the FR1 condition. The discriminability-by-delay interval "curves" were approximately parallel, suggesting no differential effect of changing the response requirement as a function of the delay value.

#### Percent Correct

As in Experiment 1, high performance at short delay values meant there was insufficient data to run an analysis of variance using the discriminability data so the percent correct data was used. The percent correct data for each condition and for each delay value are presented in Figure 17. The percent correct data follow the same general pattern as the discriminability data: a decrease in performance across conditions as the delay interval increases and a decrease as the response requirement decreases. Since bias in the data was low, the discriminability and the percent correct values were highly correlated ( $r = .94$ ). In some of the conditions, FR5, FR4, and FR3, there is a ceiling effect that was not apparent in the discriminability data. Performance was above chance levels in all conditions for each delay value, with the minimum percent correct value being 65%.

The data were transformed using an arc sine transformation (Winer, 1962) and a two-way repeated measures analysis of variance was run using Lane's program (Lane, 1981). There was a significant effect due to the conditions factor  $F(2, 7) = 6.55$ ,  $p < .025$ , and the delay factor  $F(1, 5) = 43.95$ ,  $p < .01$ . Since there was no significant interaction between the two factors, the data were collapsed across

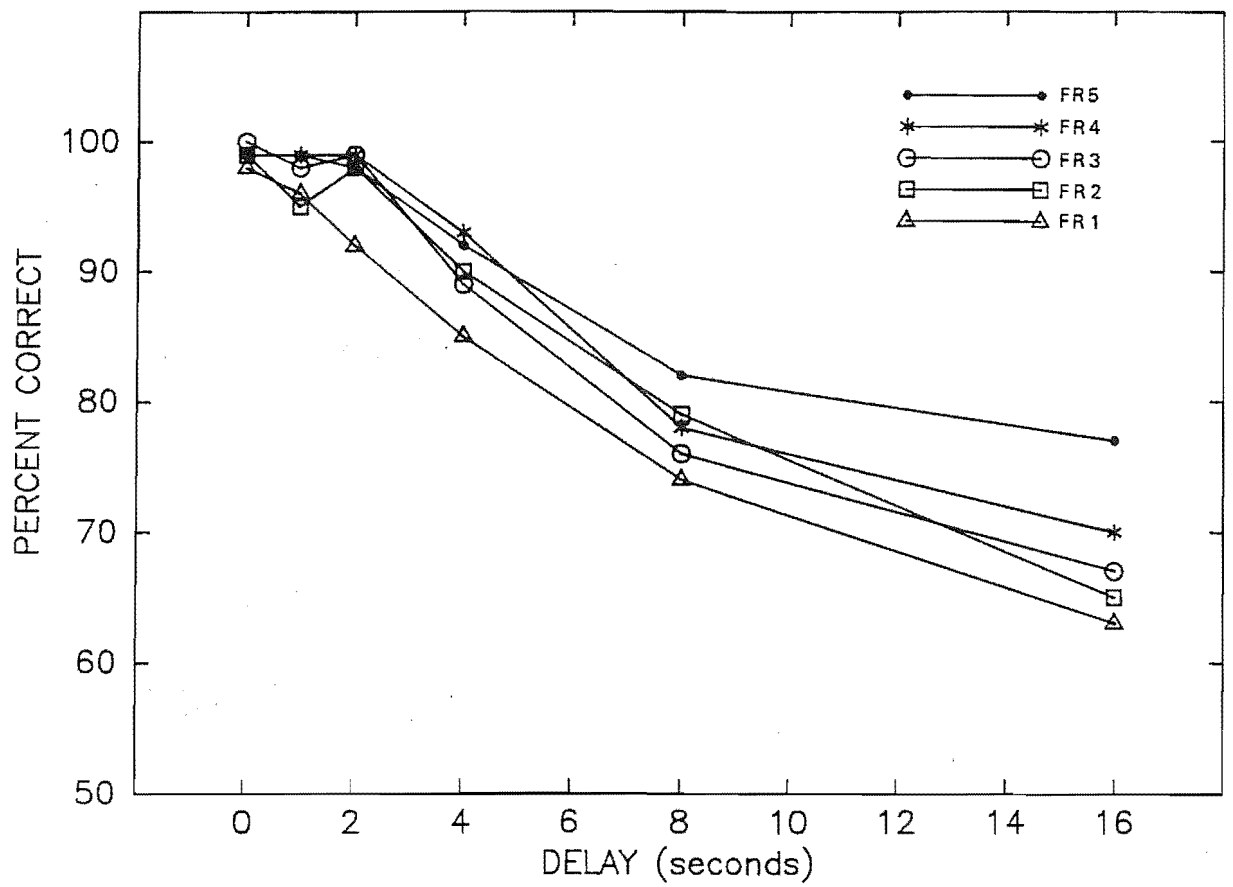


Figure 17. Percent correct for the sample stimulus conditions.



the response requirement conditions and the delay values.

Percent correct as a function of the response requirement condition is presented in Figure 18. Performance decreased consistently as the response requirement on the sample stimulus decreased. Across the conditions the average performance across all delay values decreased by only 6.6%. Compared to performance in the FR5 response requirement condition, performance in the FR2 and FR1 response requirement conditions showed a significant difference at the 1% level, assessed using Dunnett's test (Keppel, 1973).

The percent correct data pooled across the response requirement conditions are presented in Figure 19 as a function of the delay value. Performance was high at the 0, 1, and 2 second delay intervals but declined rapidly once the 4 second delay interval was reached. Performance at the 16 second delay value was 68%, well above chance level. Dunnett's test showed that performance was not significantly different from zero second delay performance until the sixteen second delay interval (1% level) (Keppel, 1973).

#### Decay Curve Functions

Both the negative exponential and the rectangular hyperbolic models of decay were fitted to the discriminability data for each of the conditions. The parameters of the best fitting equations are presented in Table 15. Both models provide a close fit to the data as indicated by the low root mean square (RMS) values. For both models the estimates of  $\log d_0$  are at a maximum in the FR5 condition, and generally decline as the response requirement decreases. The value of  $\log d_0$  was higher in the FR3 condition than in the FR4 condition, but the difference was very small. The values for  $b$  and  $h$  were stable across the conditions except for a somewhat higher rate of decrement in  $\log d$  in the FR2 condition, reflected in a slightly lower  $b$  value

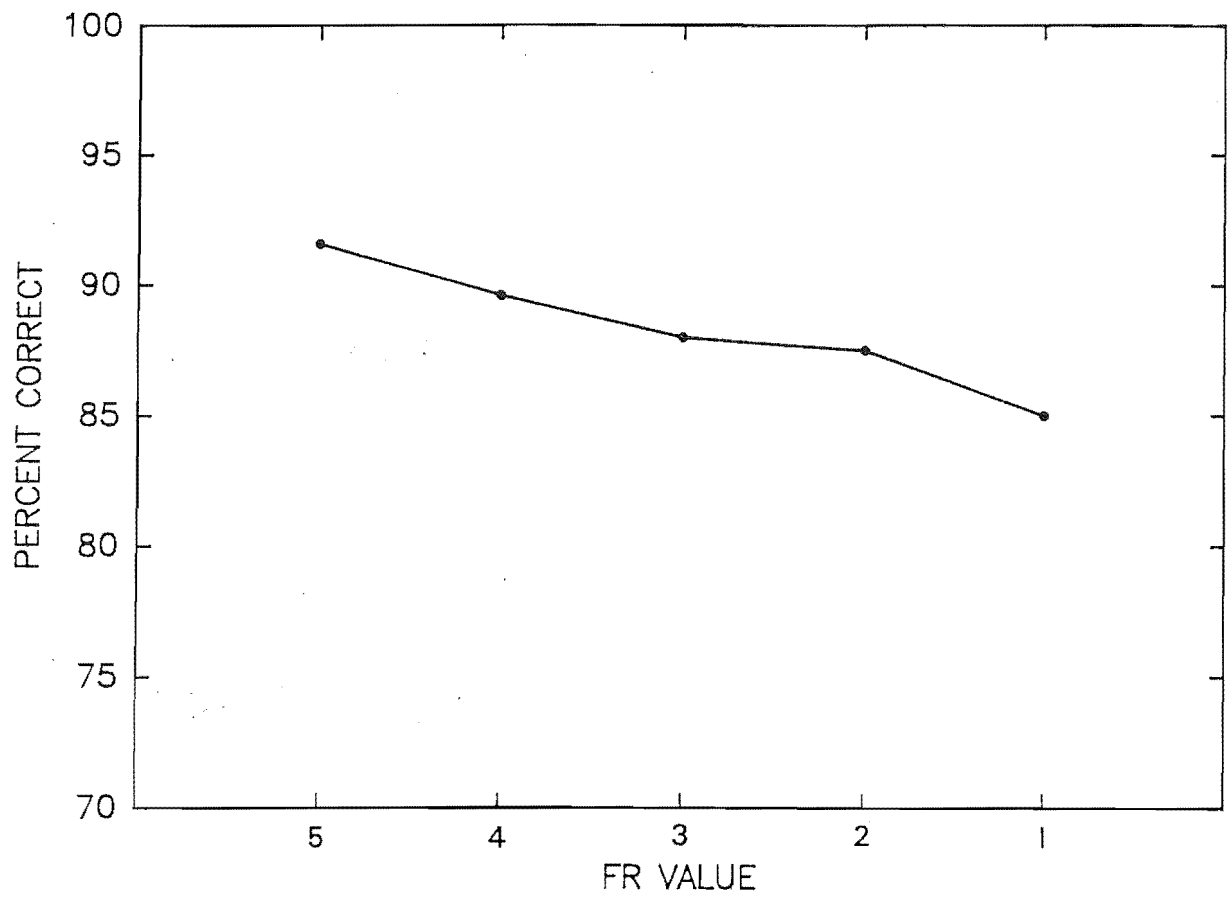


Figure 18. Mean percent correct for the sample stimulus conditions.

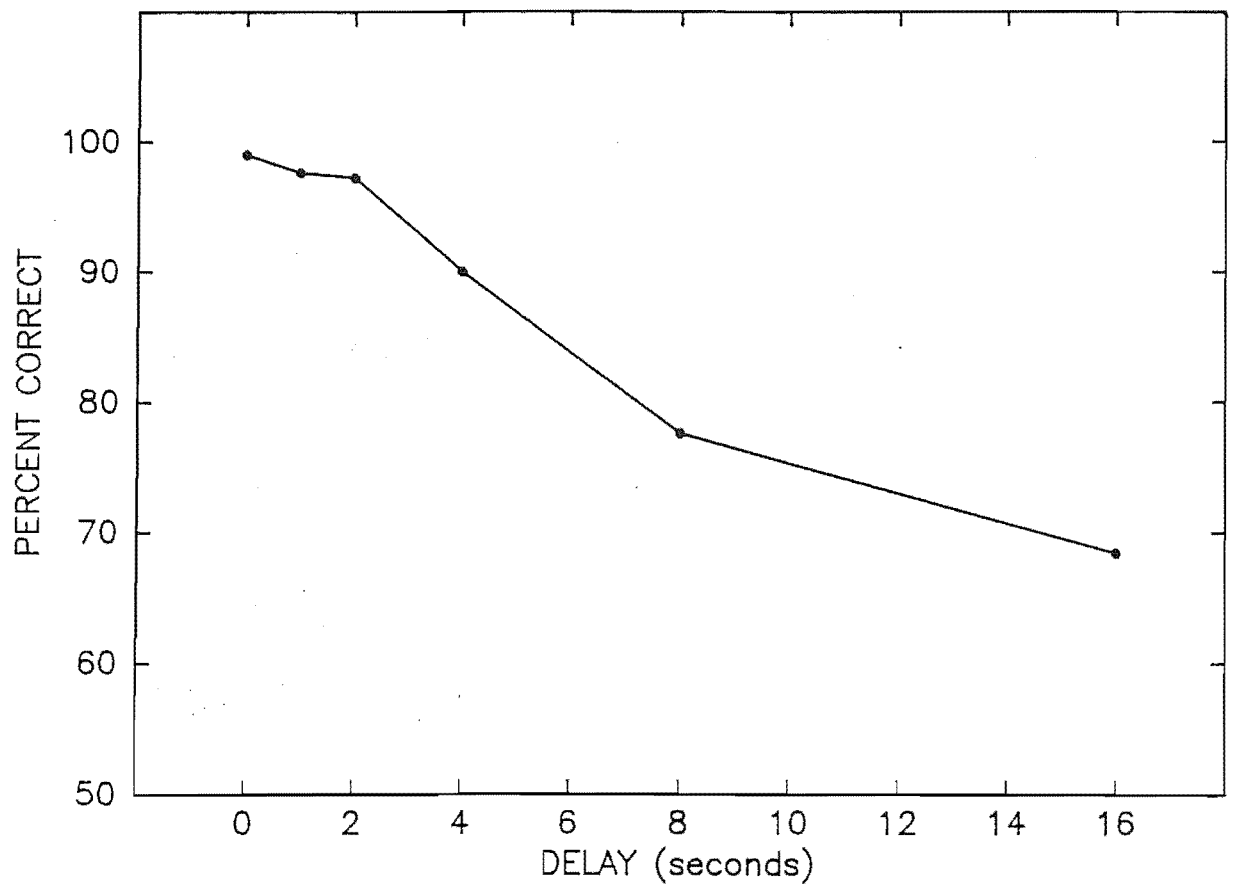


Figure 19. Mean percent correct for the delay intervals.

Table 15

Parameters of the Decay Functions for the Sample Stimulus  
Conditions

FR Value	<u>Exponential</u>			<u>Hyperbolic</u>		
	log do	b	RMS	log do	h	RMS
5	2.41	.15	.053	3.11	2.40	.010
4	2.35	.16	.028	2.82	2.75	.037
3	2.38	.18	.064	2.94	2.25	.068
2	1.75	.12	.054	1.93	4.35	.074
1	1.55	.16	.010	2.00	2.35	.001

RMS = Root Mean Square

and a slightly higher h value. In general there were no increasing or decreasing trends in the b or h values across the conditions.

This change in the initial discriminability is also seen in the pattern of the regression lines for each of the response requirement conditions which is presented in Figure 20. The lines are approximately parallel, showing changes in the initial value but no change in the slope across the conditions.

#### Comparison of Baseline 2 and Baseline 3

To assess the effects on baseline performance of exposure to the changing response requirement the sample stimulus, the baseline prior to the experiment, Baseline 2 was compared with a baseline taken after the experiment, Baseline 3. For both these baselines, a FR5 response requirement was in effect. The point estimates of discriminability for each delay value for Baselines 2 and 3 are presented in Figure 21.

While the values at the 1 second and 16 second delay values are the same in both baselines, the values for Baseline 3 are greater than for Baseline 2 at all other delay values. This increase in performance in Baseline 3 was not statistically significant,  $F(1,4) = .27$ ,  $p > .05$ .

The parameters of the best-fitting negative exponential and rectangular hyperbolic equations for the two baselines are presented in Table 16. The log do values are similar for both equations across the two baselines and there was little difference in either the rate of decay, b, or the half-life, h, values.

#### Discussion

In this experiment the response requirement on the sample stimulus was systematically varied and the subsequent effects on accuracy analyzed within the behavioural model of signal detection. As

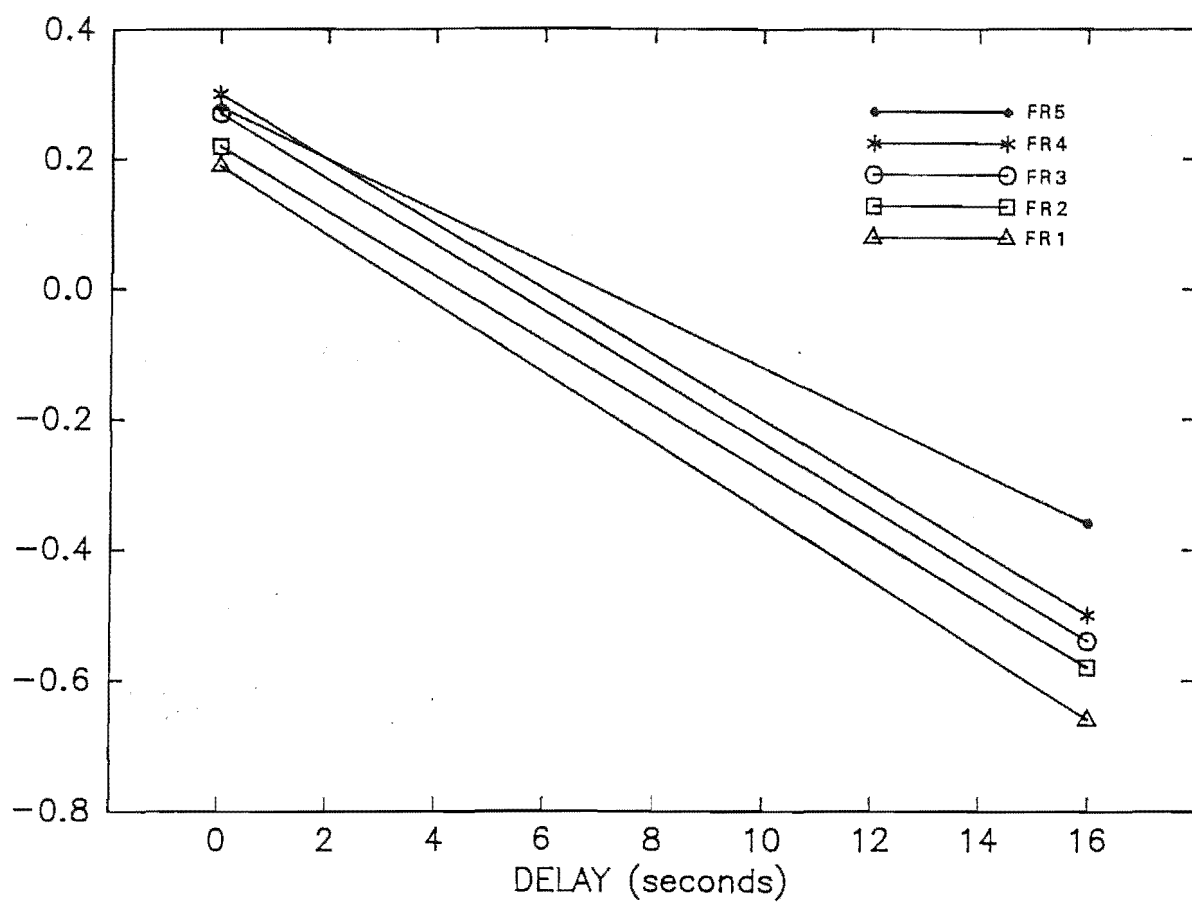


Figure 20. Regression lines for the sample stimulus conditions.

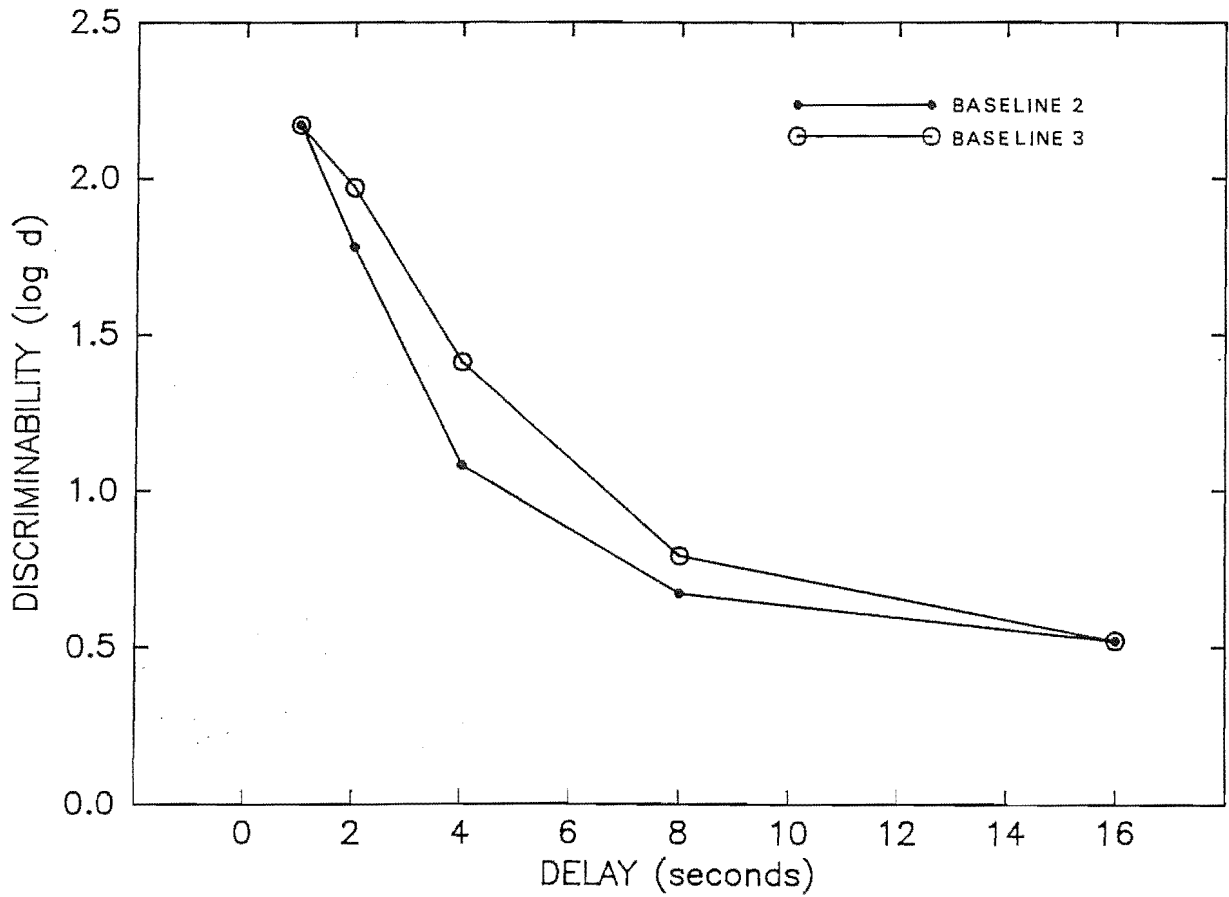


Figure 21. Point estimates of discriminability for Baseline 2 and Baseline 3.

Table 16

Parameters of the Decay Functions for Baseline 2 and  
Baseline 3

Condition	<u>Exponential</u>			<u>Hyperbolic</u>		
	log do	b	RMS	log do	h	RMS
Baseline 2	2.41	.15	.053	3.11	2.40	.010
Baseline 3	2.44	.12	.019	2.87	3.64	.011

RMS = Root Mean Square



in Experiment 1, use of the controlled reinforcement rate procedure kept bias to a minimum with all bias values being close to zero. Interestingly in this experiment while the majority of bias values were positive, indicating a consistent though small bias toward responding to the red comparison stimulus as in Experiment 1, most bias values at the lowest response requirement were negative. In this condition, presumably the discrimination was most difficult, as when the higher doses of CPZ are administered. In the case of the two highest doses of CPZ, all the bias values were positive. Whether this finding reflects fundamental differences in performance between the two experiments, or is merely due to random fluctuations in performance, cannot be determined.

The discriminability across the sample stimulus conditions declined as the delay interval increased and the response requirement decreased. The same pattern occurred in the percent correct data although here a ceiling effect was obvious at short delay values at the higher response requirements. Since bias was low, the percent correct measure gave a relatively bias-free measure of performance. As expected the analysis of variance showed a significant effect due to the delay factor. Compared to Experiment 1, performance across the delay intervals remained higher, with a significant difference from the level of performance at zero-delay not being reached until the sixteen second delay interval. The conditions factor had less effect on performance. Performance remained very high across all the sample stimulus conditions, probably due to the high baseline level of responding or because the response requirement on the sample stimulus was gradually reduced allowing the subjects an opportunity to "learn" to respond accurately to the more difficult discriminations.

In comparison to the percent correct data, the decline in the discriminability data across the response requirement conditions was

erratic at short delay values probably due to the high overall performance levels. There was no ceiling effect in the discriminability data as the maximum log d value was reached only once. There was no floor effect either as log d values remain above zero. This meant there should be no distortion in the negative exponential or the rectangular hyperbolic decay functions fitted to the data. Both the decay functions fit the data well, and show the response requirement manipulation was affecting only the initial discriminability, log d<sub>0</sub>, and not the rate of decay, b, or the half-life, h. This finding is in agreement with that of White (1985) and adds support to the general finding that procedural variations in sample stimulus characteristics affect performance by altering the initial discriminability, (i.e., performance at zero delay) and not the rate at which performance declines as a function on the delay interval.

In terms of levels of performance across the conditions, in both Experiments 1 and 2, when the parameters of the decay functions were compared, performance was most similar across two pairs of conditions. The 0.5 and 2.5 mg/kg CPZ doses led to performance levels mid-way between the FR2 and FR1 conditions in Experiment 2. performance at the lowest drug doses was comparable to that in the lowest response requirement conditions. the higher drug doses led to performance at much lower levels than in the FR1 condition. Therefore the drug impaired performance much more than the response requirement manipulation, even though the pattern of impairment was the same. greater levels of performance in the second experiment were probably partly due to the higher level of baseline performance at the start of Experiment 2, compared to performance at the start of Experiment 1. It is interesting to note that in this experiment, as in Experiment 1, the baseline level of responding was higher following exposure to the

experimental conditions. Unlike Experiment 1, there were no changes in either the initial discriminability, log do, or the rate of decay measured by the parameters of the decay functions when Baseline 2 and Baseline 3 were compared.

Changes in baseline levels of responding could be due to an overall drift in performance due to practice effects. The drift may have been occurring so slowly in Baseline 1 that performance met the stringent stability criteria. Alternatively, exposure to the drug in Experiment 1, and to changes in the sample stimulus response requirement in Experiment 2, resulted in improved performance. Exposure to the more difficult discrimination could make the subjects better able to perform the discrimination under standard conditions.

To determine the nature of this drift in performance a between groups study could be carried out. After equivalent training, group 1 would receive exposure to the drug, for example, and group 2 would continue working under standard baseline conditions for the same period of time. Any change in the performance by group 1 relative to that of group 2 could be attributed to exposure to the drug.

In summary, this experiment has shown that the effects of CPZ can be mimicked by the procedural variation of changing the response requirement on the sample stimulus. By decreasing the requirement from 5 responses to 1, the same pattern of results was achieved as when increasing doses of CPZ were administered; therefore a similar mode of action can be postulated for the drug and the sample stimulus manipulation. In both cases the analysis shows the effect on performance to be limited to the initial discriminability, and neither of the interventions change the rate at which the initial discriminability declines. The interventions can therefore be presumed to be affecting discrimination and/or encoding and retrieval processes with no effects on retention or memory. This experiment has added

support to the model of CPZ action and provides further data concerning the role of sample stimulus requirements in DMTS performance.

### Experiment 3

The results of Experiment 2 provide strong support for the model of CPZ action that proposed the drug has no specific effect on memory or retention processes and causes decreases in delayed matching performance because it decreases zero-delay performance. This suggests that it may be possible to compensate for the effects of CPZ by raising the baseline level of performance. If the discrimination was easier, zero-delay performance should be greater, so the effects of CPZ should be less, relative to a condition where the discrimination is more difficult. To make the discrimination easier, the sample stimulus response requirement can be increased. The literature reviewed earlier in this chapter shows that this will increase the level of the initial discriminability without affecting the rate of decrement of discriminability. In this experiment the response requirement on the sample stimulus was increased from FR5 to FR10 to increase the baseline level of performance. The effects of a 5 mg/kg dose of CPZ was assessed relative to the drug effects when a sample stimulus FR5 requirement was in effect (Experiment 1). The 5 mg/kg dose level was chosen since in Experiment 1 it produced a considerable decrease in performance without causing any response failure.

This experiment provided a further analysis of the model of CPZ action and also provided a useful evaluation of whether the effects of CPZ can be compensated for by a variation in the DMTS procedure.

### Method

### Subjects

The same 5 subjects were used as in Experiments 1 and 2.

### Apparatus

The same apparatus was used as in Experiments 1 and 2.

### Procedure

All the procedural variables remained identical to those in Experiment 1, except for a change in the response requirement on the sample stimulus. At the beginning of the experiment the response requirement was increased from 5 to 10 and the subjects continued on the FR10 requirement until the two stability criteria were reached (Harnett et al., 1984). Across the subjects, data from the last three sessions in the FR 10 condition were pooled and the condition labelled Baseline 4. Following Baseline 4, three administrations of a single dose of CPZ ( 5 mg/kg) were given. The injections were given as in Experiment 1. They were intraperitoneally administered, 15 minutes prior to the start of the experimental session, with the CPZ diluted with isotonic saline. "Drug" sessions continued until all trials were completed or for 90 minutes, whichever came first. Several sessions occurred between the drug injections to allow for washout. The proportion correct had to be within 0.05 of the mean portion correct during Baseline 4 before the next injection was given and this was usually within 2-4 days.

### Results

When the response requirement on the sample stimulus was increased, two of the five subjects showed response failure, i. e.,

they did not complete all the trials in a session. This was probably due to ratio strain, where the number of responses required to earn reinforcement was too great to sustain responding. For these subjects (subjects 3 and 5), the response requirement was decreased in the hope they would respond reliably at lower fixed ratios, following which the requirement could be gradually increased to 10. After several weeks at the lower fixed ratios, i.e., FR 6-8, the performance of these subjects was still erratic. They showed long pauses within sessions, and consequently almost constant failure to complete sessions within a 90-minute period. Therefore these two subjects were omitted from the experiment.

#### Performance During Baseline 4

The number of responses to red and green comparison stimuli following red and green sample stimuli for each delay value for the Baseline 4 condition is presented in Table 17. The total number of trials at each delay value was 180. Performance was perfect at the 0 and 1 second delay values and the presence of only one error at the 2 second delay value meant the point estimates of discriminability could not be calculated for the three shortest delay values. Therefore the percent correct measure was used. For these data, percent correct provides a good measure of performance as the three values of bias that were calculable were all low: -0.24, 0.12, and -.13.

A comparison of the percent correct at each delay value for Baseline 3 (FR5) and Baseline 4 (FR10) is presented in Figure 22. Only the mean data for subjects numbered 2, 3, and 5 are presented for the Baseline 3 condition. Performance in Baseline 4 is greater at the longer delay values than in Baseline 3. At the 8 and 16 second delay intervals performance is increased by an average of 10.5% in Baseline 4. There is a small increase in performance at the shorter delays

Table 17

Number of Red and Green Comparison Key Responses Following  
Red and Green Sample Stimuli in Baseline 4

FR Value	Delay	C. R.	F. A.	Miss	Hit
		GG	GR	RG	RR
10	0	90	0	0	90
	1	90	0	0	90
	2	90	0	1	89
	4	89	1	3	87
	8	85	5	3	87
	16	81	9	15	75

C. R. = Correct Rejection

F. A. = False Alarm

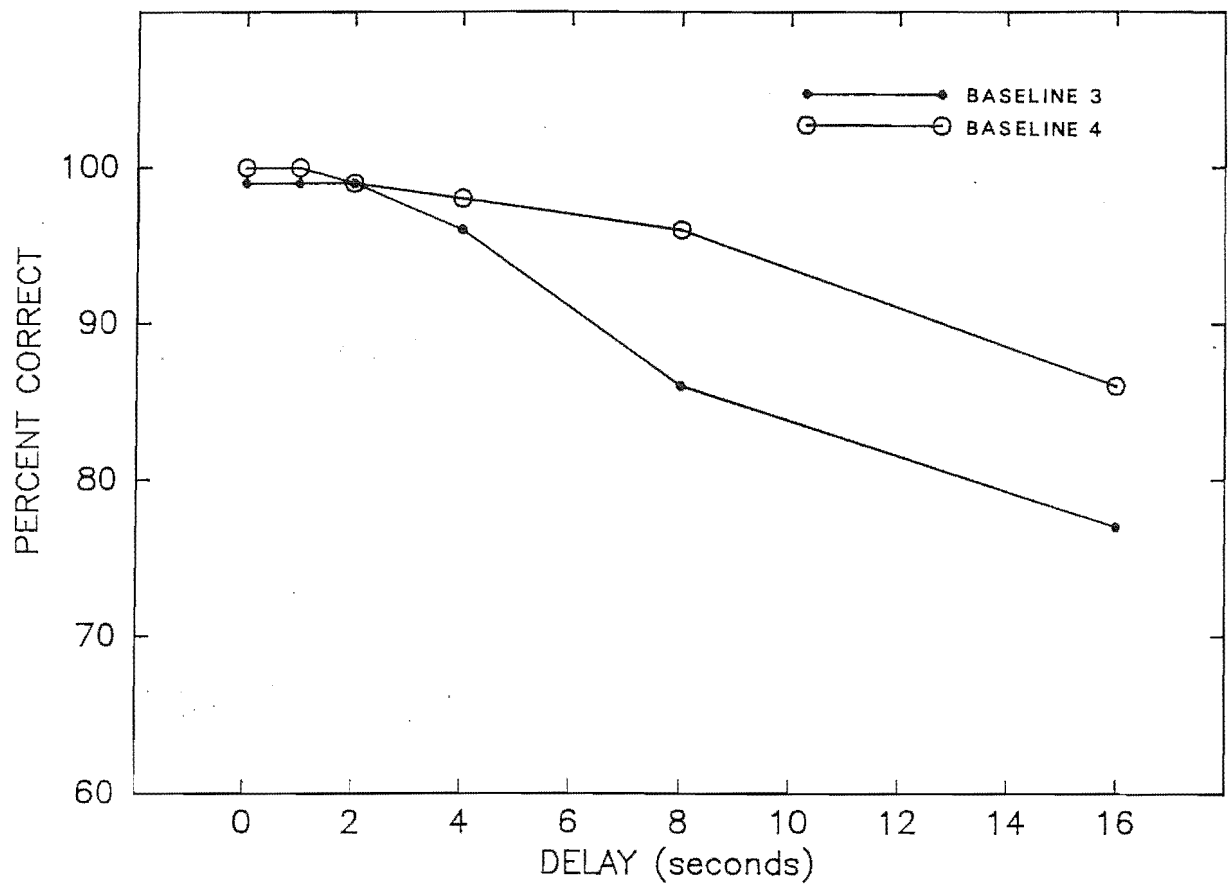


Figure 22. Percent correct for Baseline 3 and Baseline 4.



although in both conditions there is an obvious ceiling effect at the shorter delays. The overall difference in performance between the two baselines was not significant,  $F(1,2) = 9.84$ ,  $p > .05$ . There was a significant effect due to the delay factor,  $F(1,3) = 17.53$ ,  $p < .025$ , but no significant interaction.

Effects of CPZ on FR10 Responding and a Comparison with the Results of Experiment 1

To allow the data from the drug condition in this experiment, when a FR10 response requirement was in effect to be compared with that of Experiment 1, when a FR5 response requirement was in force, the data from the 5 mg/kg condition in Experiment 1 was reanalyzed to include only subjects numbered 2, 3, and 5. The number of red and green comparison stimuli responses following red and green sample stimuli responses when CPZ was administered under each of the response requirement is presented in Table 18. The total number of trials at each delay value was 180. There was no response failure in either drug condition.

Bias. There were sufficient errors at all the delay values except the zero delay value in the FR10 drug condition to calculate the point estimates of discriminability and bias. These values are presented in Table 19. Across both drug conditions bias was small with a predominance of negative values in the FR5 drug condition (indicating a bias toward the red comparison stimulus).

Discriminability. Point estimates of discriminability for the two drug conditions are presented in Figure 23. For both conditions the log d values decreased as the delay interval increased. At all delay values except the four second delay interval performance under

Table 18

Number of Red and Green Comparison Key Responses Following  
Red and Green Sample Stimuli when CPZ was Administered  
in the FR10 and FR5 Conditions

Response		C. R.	F. A.	Miss	Hit
Requirement	Delay	GG	GR	RG	RR
FR10	0	90	0	1	89
	1	88	2	2	88
	2	82	8	8	82
	4	69	21	10	80
	8	71	19	19	71
	16	64	26	19	71
FR5	0	88	2	1	89
	1	87	3	9	81
	2	81	9	10	80
	4	81	9	16	74
	8	71	19	30	60
	16	61	29	30	60

C. R. = Correct Rejection

F. A. = False Alarm

Table 19

Point Estimates of Log Response Bias Following CPZ  
Administration in the FR10 and FR5 Conditions

Delay	<u>Response Requirement</u>	
	FR10	FR5
0	-	.15
1	0	-.25
2	0	-.03
4	0.19	-.14
8	0	-.14
16	0.09	-.01

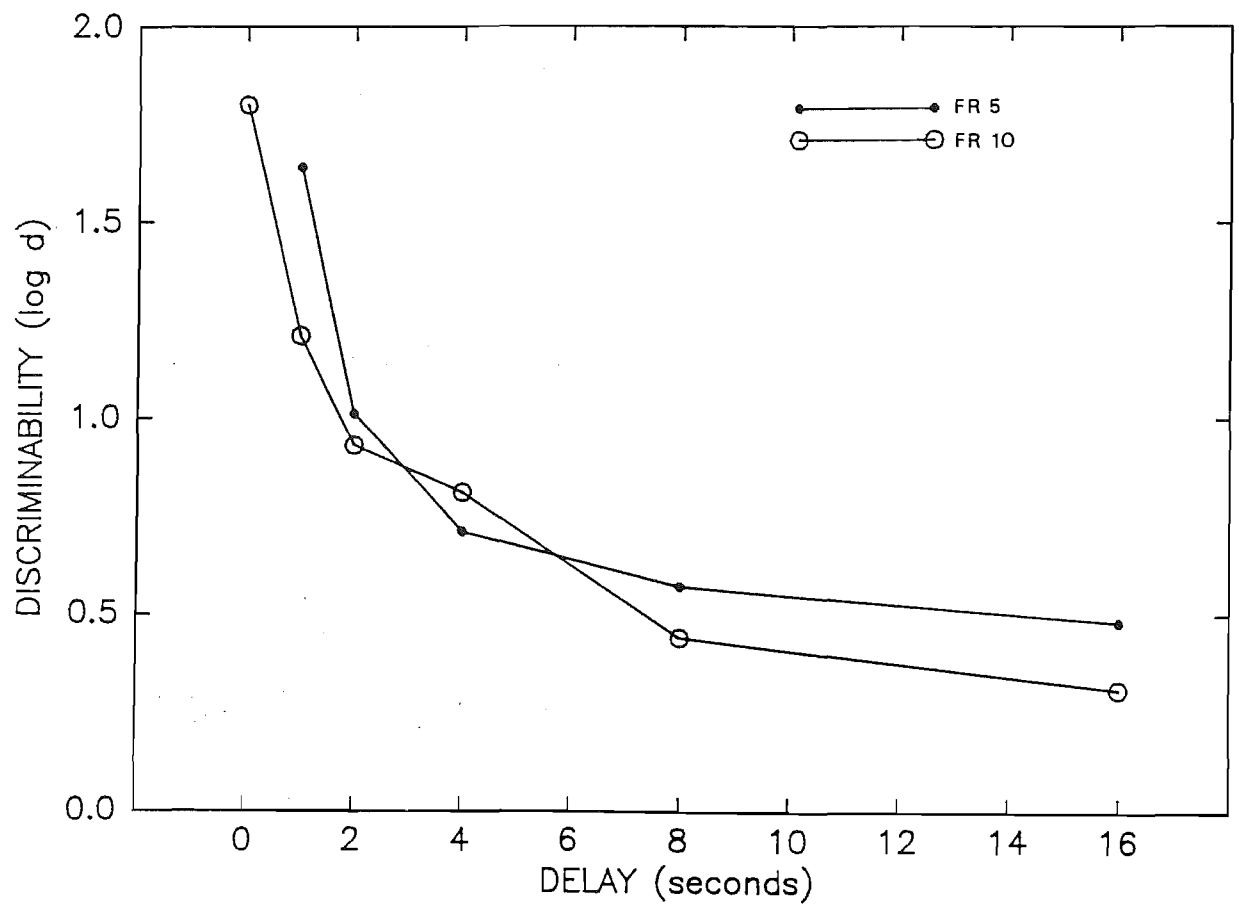


Figure 23. Point estimates of discriminability for the FR10 and FR5 drug conditions.

the drug was higher in the FR10 condition than the FR5 condition. Further analysis was carried out using the percent correct data.

Percent Correct. The percent correct for each of the drug conditions for each delay value is presented in Figure 24. The pattern of performance is similar to the discriminability data, with the exception that ceiling effects were more apparent in the FR10 condition. Since bias was low, the percent correct and log d measures were highly correlated ( $r = .94$ ). A two-way repeated measures analysis of variance showed there was no significant difference in performance under the two drug conditions,  $F(1,2) = 18.36$ ,  $p > .05$ . There was a significant effect due to the delay factor,  $F(1,2) = 50.09$ ,  $p < .025$ , but no significant interaction between the two factors.

In Figure 25 the percent correct for each drug condition is shown relative to the corresponding baseline performance for the two response requirements. (In the FR5 condition, drug performance is compared with that in the composite saline condition). The 5 mg/kg dose of CPZ caused a comparable decrease in performance across the two response requirements. Across all the delay values the drug caused a percentage decrease of 7.4% when a FR5 response requirement was in effect and a 9.2% decrease when the FR10 requirement was in effect. For both the response requirements the decrease in performance caused by the drug was not statistically significant.

Decay Functions. The negative exponential and the rectangular hyperbolic decay functions were both fitted to the discriminability data for the two drug conditions. The parameters of the best fitting curves are presented in Table 20. For both decay models the values for the initial discriminability, log d<sub>0</sub>, are considerably higher in the FR10 drug condition than in the FR5 condition. Across the two

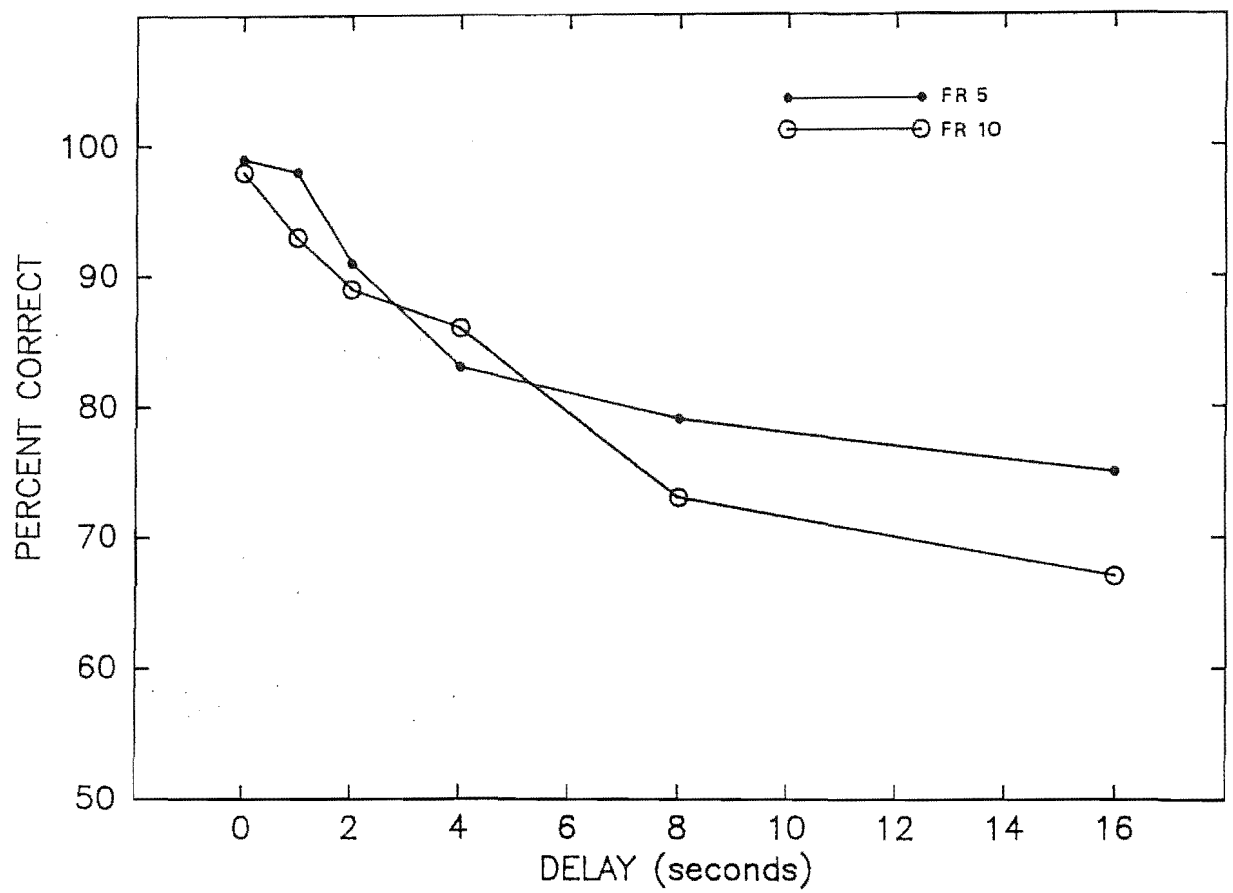
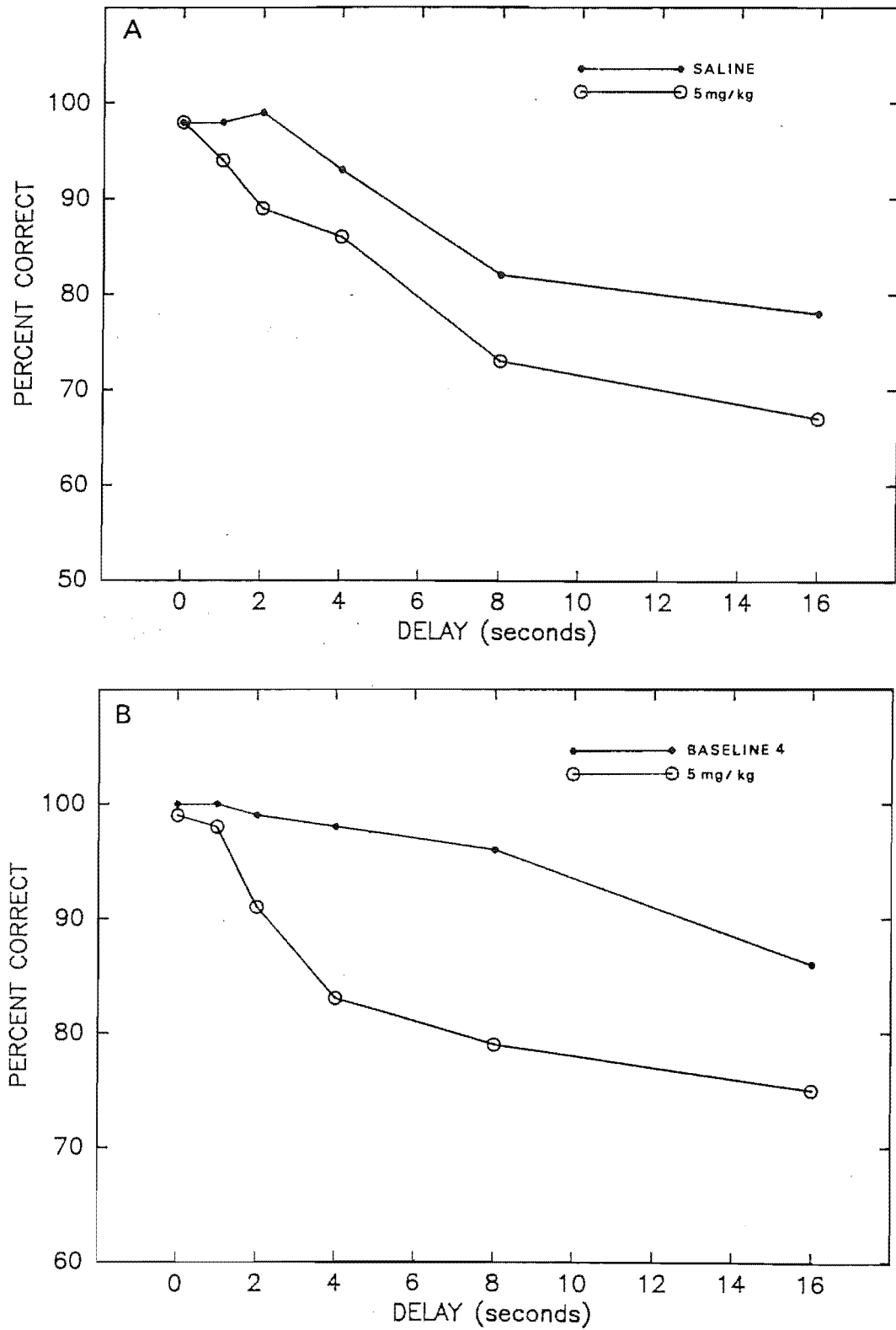


Figure 24. Percent correct for the FR5 and FR10 drug conditions.



**Figure 25.** Percent correct for baseline or composite saline and drug conditions for A. FR5 and B. FR10 sample stimulus response requirements.

Table 20

Parameters of the Decay Functions for the Two Drug Conditions

Response Requirement	<u>Exponential</u>			<u>Hyperbolic</u>		
	log do	b	RMS	log do	h	RMS
FR10	1.54	.13	.080	2.25	2.17	.032
FR5	1.27	.11	.009	1.50	3.89	.004

RMS = Root Mean Square



drug conditions, the rate of decay,  $b$ , and the half-life,  $h$ , values are similar and comparable to those found across a range of drug doses in Experiment 1 (see Table 8).

The similarity in the rates of decay across the two drug conditions is also apparent in the relationship between the regression lines for the two conditions which is presented in Figure 26. The lines are approximately parallel, with a difference in initial value somewhat less than expected on the basis of the decay function parameters.

### Discussion

In this experiment the response requirement on the sample stimulus was increased in an attempt to raise the overall level of stimulus control and reduce the effects of CPZ. The inability of two of the subjects to perform reliably at greater response requirements probably reflects their long history of responding at the FR5 requirement. In addition the subjects were working on a VR2 schedule of reinforcement for correct responses, and this coupled with the increased response requirement on the sample stimulus provided insufficient conditioned and primary reinforcers to maintain their behaviour. Of the five subjects, the two who were omitted from the study were those whose performance showed the most disruption when a procedural variation was made during the initial behavioural training phase. In addition, it was subject number 5 who did not respond to the CPZ in Experiment 1.

Unlike the percent correct measure, the discriminability measure,  $\log d$ , depends on the total number of trials which are distributed in the signal detection matrix. Since only three subjects completed this experiment, in order to compare Baseline 4 with Baseline 3, the

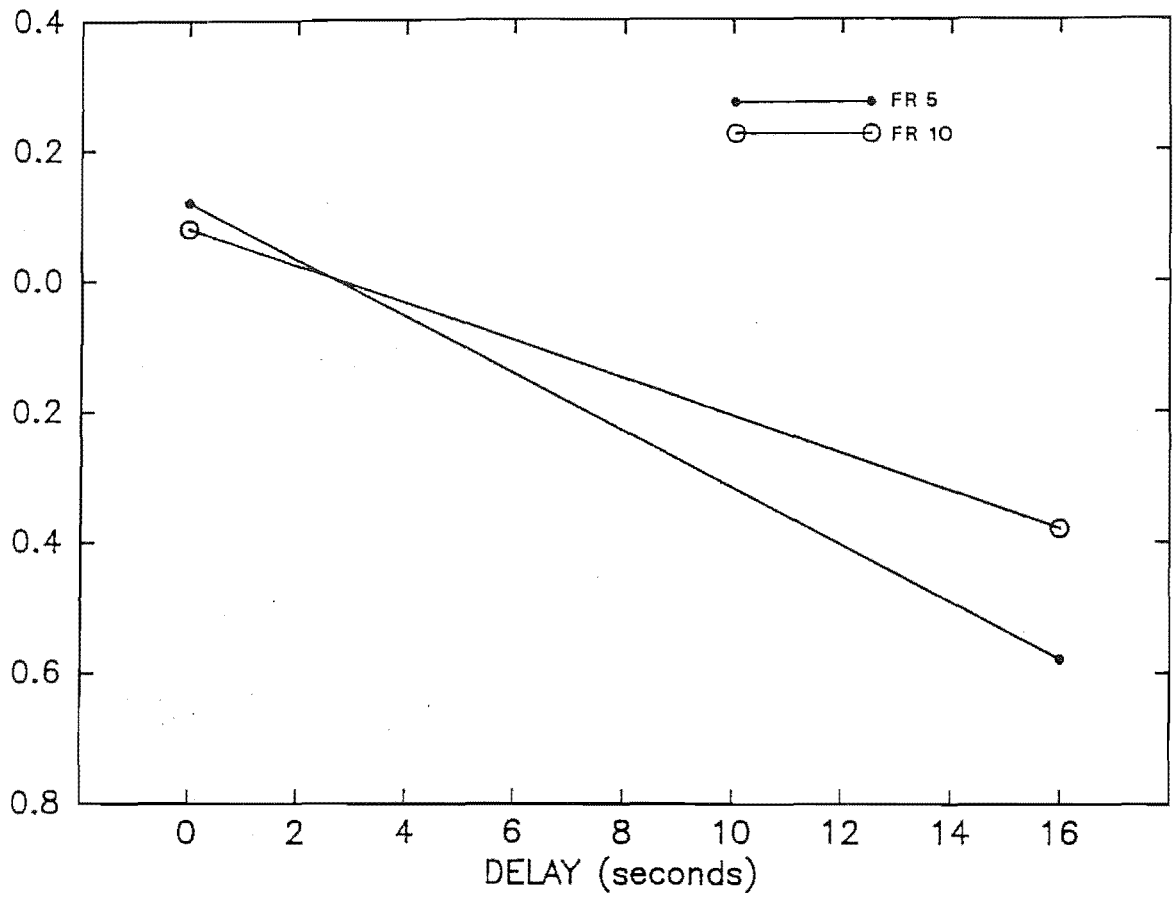


Figure 26. Regression lines for the FR5 and FR10 drug conditions.

Baseline 4 data were reanalyzed using only the data from subjects numbered 2, 3, and 5. The same recalculation of data was necessary to compare the data in the results from the drug condition in this experiment with the results of Experiment 1.

In this experiment, as in Experiments 1 and 2, the controlled reinforcement rate procedure kept bias to a minimum and meant the percent correct measure was providing a relatively bias-free measure of performance. The FR10 response requirement on the sample stimulus caused the expected increase in performance, especially at the longer delay values. At the shorter delay values there was little room for improvement. This ceiling effect may account for the lack of a significant difference in performance across the two baselines. Had performance in Baseline 3 been lower, it may have allowed more room for improvement in the Baseline 4 condition. Performance was maintained at a very high level in Baseline 4 at the longer delays; at the 16 second delay performance only decreased to 86%. It is likely therefore that performance could have been maintained above chance level for long delay intervals, perhaps up to 25-30 seconds.

The administration of CPZ caused a decrement in responding relative to the Baseline 4 level of responding. The analysis of the discriminability decay functions showed the rate of decrement in discriminability across the delay values was similar to that in Experiment 1, indicating that the increased response requirement had not altered the effect the CPZ was having on the rate at which discriminability declined. The most important finding in this experiment is the difference in the estimate of log do across the two drug conditions. The initial discriminability was greater in the FR10 drug condition than in the FR5 condition, despite the overall difference between the two conditions not being statistically significant.

A comparison of the relative decrease caused by the drug under the two response requirements showed that the drug had a similar effect on FR5 and FR10 performance. Therefore the greater absolute performance level was due to the higher baseline level of responding in the FR10 condition. This is an important finding as it suggests that drug effects on discrimination and memory tasks can be compensated for by making the task easier. In this experiment the easier task raised the level of baseline responding, and although the relative drug effects were the same as when the task was more difficult, it meant the absolute level of performance was higher. Further the results showed that this increase in the absolute performance level was due to a change in the initial discriminability and not due to changes in the rate at which discriminability declined. This result needs to be replicated as the data used in the analysis came from only three subjects. Despite this limitation the results of this experiment add further support to the model of CPZ action, and provide a useful starting point for devising ways to overcome drug induced impairment in a clinical situation. This issue will be discussed further in Chapter 7.

## CHAPTER SIX

### The Effects of Haloperidol on Discrimination and Memory Processes

#### Introduction

Haloperidol, an antipsychotic drug belonging to the butyrophenone class, was first synthesized in the Belgium laboratories of Paul Janssen in 1956. It was clinically tested in 1958 and made available for psychiatric use in 1960 (Janssen, 1967). Haloperidol was the first high potency antipsychotic to be discovered. In terms of dose equivalence, a 100 mg/kg dose of CPZ has the same therapeutic efficacy as a 1.6-2.0 mg/kg dose of haloperidol (Davis, 1974).

When first discovered, haloperidol was believed to have greater specificity for the treatment of florid psychotic symptoms, but no clinical support was found for these proposed differences (Mason & Granacher, 1980). What is known is that compared to CPZ, haloperidol is faster and longer acting. Along with other high potency antipsychotics (fluphenazine, thiothixene, perphenazine, and trifluoperazine) haloperidol does not have the hypotensive and general depressant effects of the low potency drugs like CPZ and thioridazine (Benet & Sheiner, 1980; Janssen, 1980; Mason & Granacher, 1980).

Apart from its psychiatric use, haloperidol is used as an anti-emetic in internal medicine and in neurology in the treatment of Gilles de la Tourette syndrome which consists of multiple tics and coprolalia (van Praag, 1978; J.H. White, 1977). In pediatric psychopharmacology, the drug is widely used in the treatment of autism, hyperactivity, aggression and conduct disorders, as well as for "behavioural management" in the mentally retarded (Werry, 1978).

The effect of haloperidol on cognitive performance has been

investigated. Werry and Aman (1975) found that haloperidol administered to hyperactive subjects in low doses (.025 mg/kg) improved cognitive function but a higher dose of .05 mg/kg caused a deterioration. Recent research by Campbell and her associates has found that cognitive impairments are not an effect of the drug per se but of the dose level. In a study where haloperidol was administered to autistic subjects, it was found that doses that decreased behavioural symptoms facilitated learning of a discrimination task. Further the facilitation was due to a direct effect on learning mechanisms rather than the result of a decrease in maladaptive behaviors (Campbell, Anderson, Small, Perry, Green, & Caplan, 1982).

This is an important finding and suggests that antipsychotic drugs may differ in their relative effects on behavior and cognitive functioning. Whether or not antipsychotic drugs disrupt cognitive functioning depends in all probability on their anticholinergic effects (Werry, 1980). The cholinergic system has been implicated in the control of memory functioning (Carlton, 1963). Cognitive effects would be predicted to be greatest with the more sedative antipsychotics, i.e., the low potency drugs such as CPZ and thioridazine (Werry, 1982). Clinically therefore, there is some encouraging evidence that drug-induced cognitive impairment may be dose-dependent and that high potency drugs such as haloperidol may be less likely to cause such impairment. What follows is a brief review of the effects of haloperidol on learning and discrimination tasks in animals.

#### Escape and Avoidance Responding

The effects of haloperidol have been determined using both discrete-trials and continuous avoidance procedures. Generally, at low dose levels the drug produces a powerful inhibitory effect on learned

shock avoidance performance. For example, using a discrete-trials pole jump procedure with rats, Davies and Redfern (1974) found haloperidol (50 and 200 ug/kg) significantly inhibited the acquisition of the conditioned avoidance response. Using a similar procedure Davies, Jackson and Redfern (1973) found haloperidol (200ug/kg) decreased the number of correct responses by approximately 55% one hour after injection and a maximal disruption of 65% was seen after two hours.

A discrete-trials procedure using a "jumping box" has been used with dogs (Cohen, 1981; Janssen & Niemegeers, 1961; Niemegeers & Janssen, 1960, 1965). The two studies by Niemegeers and Janssen found a dose-dependent increase in avoidance impairment (Niemegeers & Janssen, 1965), and an increase in avoidance latency at lower doses (0.005 and 0.02 mg/kg) and significant inhibition of escape behaviour at 0.08 mg/kg (Niemegeers & Janssen, 1960).

Several studies have used Sidman avoidance procedures to compare the effects of haloperidol and CPZ. For example, Niemegeers, Verbruggen and Janssen (1969a) studied the effects of various neuroleptic drugs in rats using a lever press shock-avoidance procedure. Haloperidol (0.005-0.16 mg/kg) caused a dose-dependent decrease in the response rate and the percentage of shocks avoided. A similar pattern of results was obtained for CPZ (0.08-2.5 mg/kg). The ED50 values obtained were 0.03 mg/kg for haloperidol and 1.2 mg/kg for CPZ again illustrating the more potent nature of haloperidol. Using a slightly different procedure Niemegeers et al. (1969b) trained rats on the same procedure as the previous study, then alternated avoidance conditioning and extinction periods during a one hour session. Again the same pattern of results was obtained for both haloperidol (0.02, 0.04 and 0.08 mg/kg) and CPZ (0.16, 0.63 and 2.5 mg/kg) with the ED50 values for the reinforcement and extinction periods being 0.72 and 0.041 mg/kg for haloperidol and 1.4 and 0.67 mg/kg for CPZ.

Herman et al. (1979) compared the effects of haloperidol (0.25, 0.5, and 1.0 mg/kg) on a discrete-trials avoidance procedure (shelf jumping) and a lever press continuous avoidance procedure. In both procedures haloperidol decreased the percentage of avoidance responses in a dose-dependent manner with the minimum effective dose (i.e., the lowest dose producing a statistically significant decrease in avoidance responding being 0.5 mg/kg for the lever press procedure and 1.0 mg/kg for the shelf jump procedure). This study again illustrates the greater sensitivity of continuous avoidance procedures to drug effects.

#### Free-Operant Discrimination Procedures

Several authors have found that on a MULT FR FI schedule haloperidol decreased FI responding at doses lower than that required to decrease FR responding (Barrett, 1983; Bignami & Ghatti, 1969; Leander, 1975; Wenger, 1979). In two studies where pigeons were used as subjects, FI responding was decreased by doses of haloperidol as low as 0.03 mg/kg while FR responding did not decrease until the dose was 0.3 mg/kg (Barrett, 1983; Leander, 1975).

While this finding is essentially the same as that for CPZ, haloperidol appears not to have the characteristic rate-dependent effects that CPZ exhibits. Bignami and Ghatti (1969) worked with pigeons on a MULT FR33 FI5min schedule but only reported on the FI performances. (The FR component served as a control for the physical ability of the animals to peck at a high rate and the ability to discriminate between the visual stimuli signalling the two components of the multiple schedule). Haloperidol (0.05, 0.1, 0.2, 0.4 mg/kg) resulted in no changes in the quarter life values. It did cause an increase in pausing (the time between the beginning of the intervals and the resumption of responding) and this coupled with a reduction in



the response rate meant the relative distribution of responses in various portions of the FI was unaltered. This result was confirmed by Leander (1975) using pigeons and Wagner, Masters, and Tomie (1984) using rats.

One study has provided evidence of a rate-dependent effect with haloperidol. Wenger (1979) used a MULT FR30 FI600sec schedule with mice and pigeons as subjects and various doses of haloperidol (0.008, 0.027, 0.08, 0.27, 0.8, and 2.7 umoles/kg). In both species, haloperidol decreased the response rate during the FI component, and in pigeons low doses (below 0.27 umoles/kg) did not produce rate-dependent effects, but at 0.27 and 0.8 umoles/kg, a rate-dependent effect was observed. In the mouse the rate-dependent effects were also present but of smaller magnitude. The reason for the different results between the Wenger (1979) and Leander (1975) studies is unclear but it is unlikely that the procedural differences would have caused such a qualitative difference.

#### Discrete-Trials Delayed Discrimination Procedures

The effects of haloperidol on memory in monkeys and pigeons has been investigated using delayed discrimination procedures. Bartus (1978) used a delayed response procedure with monkeys to evaluate the effects of haloperidol at zero-delay and at longer delays. The monkeys sat facing nine stimulus-response panels which could be illuminated with green light. Each trial began with one stimulus panel flashing twice followed by one of three retention intervals: zero, 15, or 30 seconds, during which a screen between the monkey and the panels prevented responding. At the end of the retention interval, the screen was lowered and if the monkey responded to the correct stimulus panel it was reinforced. If the response was incorrect the screen was raised and the next trial programmed.

Five doses of haloperidol were assessed: 0.006, 0.009, 0.0125, 0.025, and 0.05 mg/kg. The results showed a progressive decrease in performance as the retention interval was increased and the dose of haloperidol increased. Analysis of variance showed a highly reliable effect for both retention interval and dose alone but no dose by retention interval interaction. Even at the 0.05 mg/kg dose level, which was so disruptive none of the monkeys completed their trials, accuracy only fell to 60% (where chance performance would be an accuracy level of 11%). It was concluded that haloperidol did not affect stimulus control or STM as assessed by the procedure and the nonspecific effects of haloperidol most likely represented some general dysfunction.

Nielsen and Appel (1983) used a delayed response procedure to investigate the effects of haloperidol in pigeons following a variable delay period. Either coloured or non-coloured light was presented on the centre key for 20 secs following which the two side lights were illuminated with red light. A correct response following noncoloured light was a right key peck and a correct response following coloured light was a left key peck. If the overall percent correct increased above 80%, one second was added cumulatively after each stimulus presentation, if performance fell below 80%, one second was subtracted from the delay and if the subject did not attain 80% correct, the delay was not in effect. Haloperidol (0.5, 1.0, and 2.0 mg/kg) caused a non-significant reduction in the overall percent correct, even at doses that caused non-responding in some subjects.

#### Delayed Matching-to-Sample

Poling, Picker and Thomas, (1984) used a DMTS procedure to evaluate the effects of haloperidol in pigeons. The pigeons responded with five pecks to a red or blue-green center key, and then after an

interval of variable delay (0.5, 1, 2, 4, or 8 seconds) responded to the matching colour when the side keys were illuminated. Every second correct match resulted in three seconds access to grain followed by a 10 second ITI. Correct matches not followed by food were followed by a 1 second flash of the hopper light. An incorrect match darkened the keys and initiated the 10 second ITI.

Haloperidol (doses 0.13, 0.25, 0.38, 0.5 mg/kg) did not consistently impair accuracy at any delay value. Percent correct responses when haloperidol was given typically approximated control values at the three shortest delay values and in 17 out of 24 instances, exceeded control values at the two longest delays. In 2 of the 3 subjects haloperidol produced a dose-dependent decrease in the rate of responding and inconsistently affected the response rate of the third subject. The number of trials completed showed a decrease with increasing doses of haloperidol. The mean number of trials completed by the three birds in the control condition was 280, in the 0.25 mg/kg condition it was 226 and in the 0.50 mg/kg condition the mean number of trials completed was 164. The study also looked at the effects of two other neuroleptics. Trifluoperazine, a phenothiazine like CPZ, generally impaired the pigeons accuracy in performing the delayed matching-to-sample task as did chlorprothixene, a thioxanthene. The authors concluded that while the butyrophenone, haloperidol, did not strongly affect responding in tasks involving recent memory, other neuroleptics may do so.

The titrating delayed matching-to-sample procedure (Cumming & Berryman, 1965) has been used to assess the effects of haloperidol in pigeons (Woodward, Watson, Blampied & Singh, 1986). Pigeons worked in a standard three key chamber where they matched the colour of the centre key (sample stimulus) with colours presented on the side keys (comparison stimuli). The delay between the sample stimuli being

extinguished and the comparison stimuli being illuminated began at zero seconds and was titrated according to the subjects performance. Two successive correct matches resulted in an increment in the delay interval by half a second, while an incorrect match resulted in a decrement of the delay interval by half a second. The delay sustained by the subjects during baseline increased until it reached a stable level at which the subjects were getting two-thirds of the trials correct. The limit of delay was defined as the longest delay value at which the subjects achieved two successive correct matches.

A single dose of haloperidol (0.5 mg/kg) caused a significant decrease in the mean limit of delay and in the mean number of trials completed. There was no change in the drug condition in the percentage correct, the position preference (the percentage of left key responses), the sample key latency (a measure of the speed at which the subject completed five pecks on the sample stimulus) or the comparison key latency (a measure of the time between the comparison stimuli becoming illuminated and the subject making a response). While the limit of delay decreased significantly, suggesting an effect on stimulus control or memory, the percentage correct measure did not decrease. The number of trials completed did decrease and it is likely that this is why the limit of delay also decreased. The limit of delay variable is not a "pure" measure of discriminability and is confounded by drug effects on psychomotor performance. This means that two subjects can end a session with the same limit of delay but having reached that delay with different behavioural patterns. For example, subject X may work at 100% accuracy but not complete the required number of trials and subject Y may complete all trials but at less than 100% accuracy and obtain the same limit of delay as subject X. So while the limit of delay cannot give any reliable results concerning the effects of haloperidol the other variables monitored do. The

results are similar to those of Bartus (1978) and Poling et.al., (1984) in that accuracy appeared to be unimpaired (there was no significant decrease in the percentage correct) but there was a psychomotor effect shown by the decreased number of trials that were completed.

#### Signal Detection Analysis

One study has used an SDT analysis to evaluate the effects of haloperidol. Hernandez and Appel (1980) used a two choice successive discrimination procedure where rats were trained to discriminate the presence or absence of a weak foot shock. Haloperidol (0.1 mg/kg) altered discriminative responding by decreasing B' (response criterion), but produced no changes in A' (sensitivity). That is, while the rats were able to accurately detect the presence of the shock following haloperidol, they tended to respond on no-shock trials.

#### Summary

While there is some evidence that haloperidol affects the control stimuli have over responding (i.e., its effects on escape and avoidance responding and multiple schedule performance), analysis of discrete-trials performance suggests that it has little if any effect on performance in delayed discrimination procedures. There is a much greater effect on response speed than discrimination or memory performance. Therefore in clinical terms the drug may achieve behavioural changes at doses that do not cause any cognitive side effects. Such a drug would be extremely useful when compared to drugs like CPZ which cause significant cognitive impairment at doses that do not cause a decrease in behavioural functioning.

#### Experiment 4

The aim of this experiment was to use the behavioural model of signal detection to assess the effects of haloperidol. The doses of haloperidol were chosen to be approximately equivalent to the doses of CPZ used in Experiment 1. When the ED50 values for the drugs are compared, the dose equivalence of haloperidol (in relation to CPZ) is approximately equivalent to that when the drugs are compared in terms of therapeutic efficacy (Niemegeers et al., 1969a). For example, 5 mg/kg of CPZ is equivalent to 0.1 mg/kg of haloperidol, and 12.5 mg/kg of CPZ is equivalent to 2.5 mg/kg of haloperidol. The 0.5 mg/kg dose was included to allow comparison of the results with other studies (Nielsen & Appel, 1983; Poling et al., 1984).

#### Method

##### Subjects

Five experimentally naive homing pigeons were used as subjects. They were housed in exactly the same conditions as detailed in Experiment 1. The subjects were numbered 6-10.

##### Apparatus

The same apparatus was used as described in Experiment 1.

##### Procedure

Behavioural procedure. The subjects underwent the same initial training as described in Experiment 1. For the experimental phases they worked on the controlled reinforcement-rate DMTS procedure. The experimental phases did not begin until the subject's performance met the two stability criteria (Harnett et al., 1984).

Pharmacological procedure. Initially a drug trial was begun testing three doses of haloperidol: 0.1, 0.25, and 0.5 mg/kg. The order of presentation of doses was randomized for each subject. Haloperidol was obtained from commercial suppliers in 5 mg/ml, 1 ml ampoules. The solution was buffered in a citric acid base to a pH of 3.2 and filtered. Injections were administered in a volume of 1 ml/kg, intraperitoneally, 15 minutes prior to the start of the experimental session. On the day immediately preceding each drug injection, a vehicle control injection was administered (acid buffered saline). Between each drug injection and the next saline injection there were at least two washout days. The proportion correct had to be within 0.05 of the mean proportion correct during baseline before the next injection was administered. Each "drug" session continued for 90 minutes or until all the trials were completed, whichever came first.

Following three injections in this series it was apparent that the doses being tested were having a widely differing effect on the subjects. For example, while subject number 8 would complete all trials in a session when given a dose of 0.5 mg/kg, the other subjects showed response failure at the lower doses. Therefore the initial drug trial was abandoned and an individual dose level for each subject was determined. This was done by changing the dose level by a 0.01 mg/kg increment or decrement until a dose level was reached where each subject was completing all 120 trials in a session within 90 minutes.

The drug levels determined for each subject were subject number 6 - .06 mg/kg, subject number 7 - .09 mg/kg, subject number 8 - .30 mg/kg, subject number 9 - .20 mg/kg, and subject number 10 - .07 mg/kg. A stable level of baseline responding was then reestablished before a second drug trial was run. Each subject received six injections at their dose level administered in the manner previously

described. Control injections were given on the days preceding each drug injection.

## Results

The results are presented in two sections. First the effects of vehicle control injections and secondly the effects of haloperidol on variables assessing psychomotor and matching performance. Data are presented from the second drug trial and the baseline period immediately preceding that trial.

### The Effect of Saline Injections on Performance

Data were pooled across the five subjects for the last six days of the baseline phase and the six days on which saline injections were administered.

Measures of Psychomotor Performance. One variable assessing psychomotor performance was response failure (when a subject did not complete all 120 trials in a session). There was no response failure for any subject during any of the baseline or saline sessions.

The mean centre key latency and side key latency values across the five subjects are presented in Table 21. A two-way repeated measures analysis of variance was carried out for both sets of data. For the centre key latency data, there was no significant effect due to the conditions or the delay factor. For the side key latency data there was a significant effect due to the conditions factor,  $F(1,4) = 14.67$ ,  $p < .05$ , with the latency being greater in the saline than in the baseline condition. There was no significant effect due to the delay factor or the interaction of the condition and delay factors.



Table 21

Mean Centre Key Latency (CKL) and Side Key Latency (SKL)  
(sec) Across Baseline and Saline Conditions for Each  
Delay Interval

Delay	CKL		SKL	
	Baseline	Saline	Baseline	Saline
0	2.80	2.92	1.41	1.46
1	2.90	2.92	1.42	1.46
2	2.84	2.87	1.36	1.50
4	2.76	2.97	1.51	1.63
8	2.83	3.02	1.51	1.63
16	2.89	1.99	1.43	1.60

Bias. The number of responses made to red and green comparison stimuli following red and green sample stimuli for the baseline and saline conditions is presented in Table 22. The maximum number of entries at each delay interval was 600. There were sufficient entries in the error cells of the signal detection matrix to allow the point estimates of bias to be calculated for each delay value in the two conditions. The bias values are presented in Table 23. The values ranged from  $-.11$  to  $+.29$ . Just over half (58%) of the values were positive representing a bias toward responding to the red comparison stimulus. The bias values for the saline condition were lower in terms of absolute value than those for the baseline condition, with the mean absolute values being  $0.05$  and  $0.13$  respectively.

Discriminability. Point estimates of discriminability were calculated for each condition and for each delay value and are presented in Figure 27. For both conditions the discriminability decreased as the delay interval increased. In neither of the conditions was the maximum  $\log d$  value ( $2.48$ ) attained. The discriminability remained above chance level for both conditions with all discriminability values being greater than zero. For all but the zero delay interval the value of  $\log d$  was greater in the saline condition than in the baseline condition. As in previous experiments, it is not possible to carry out an analysis of variance using the discriminability data as a value is not calculable for each subject at the short delay values. Further analysis was completed using the percent correct data.

Percent correct. The percentage of trials on which a correct matching response was made in the baseline and saline conditions is presented in Figure 28. These data show the same overall pattern as

Table 22

Number of Red and Green Comparison Key Responses  
Following Red and Green Sample Stimuli for the  
Baseline and Saline Conditions.

Condition	Delay	C. R.	F. A.	Miss	Hit
		GG	GR	RG	RR
Baseline	0	297	3	5	295
	1	291	9	13	287
	2	287	13	8	292
	4	262	38	11	289
	8	227	73	47	253
	16	220	80	99	201
Saline	0	295	5	6	294
	1	298	2	3	297
	2	293	7	6	294
	4	276	24	16	284
	8	244	56	52	248
	16	231	69	66	234

C. R. = Correct Rejection

F. A. = False Alarm

Table 23

Point Estimates of Log Response Bias for the Baseline  
and Saline Conditions for Each Delay Interval

Delay	Condition	
	Baseline	Saline
0	-.11	-.04
1	-.08	-.09
2	.11	.03
4	.29	.09
8	.12	.02
16	-.07	.01

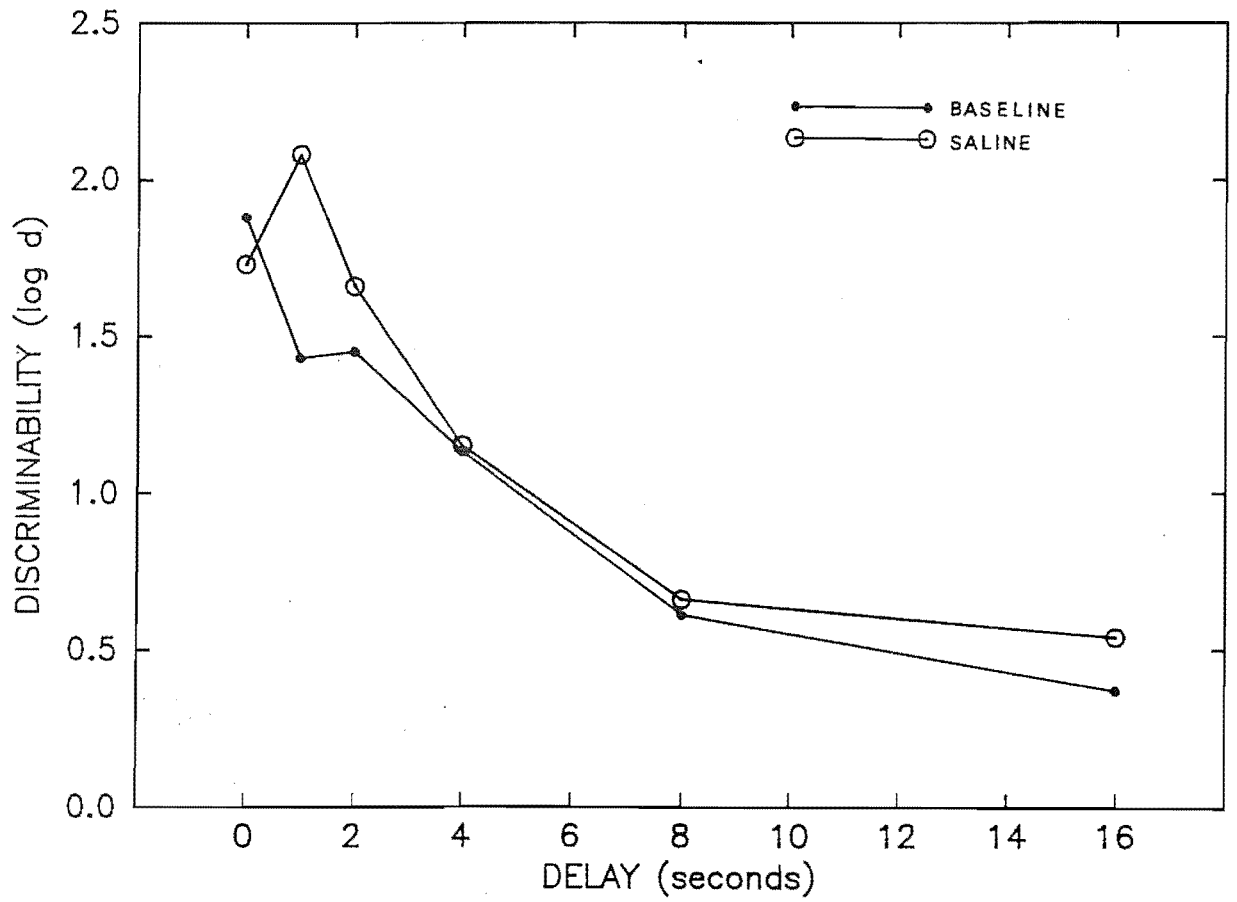


Figure 27. Point estimates of discriminability for the baseline and saline conditions.

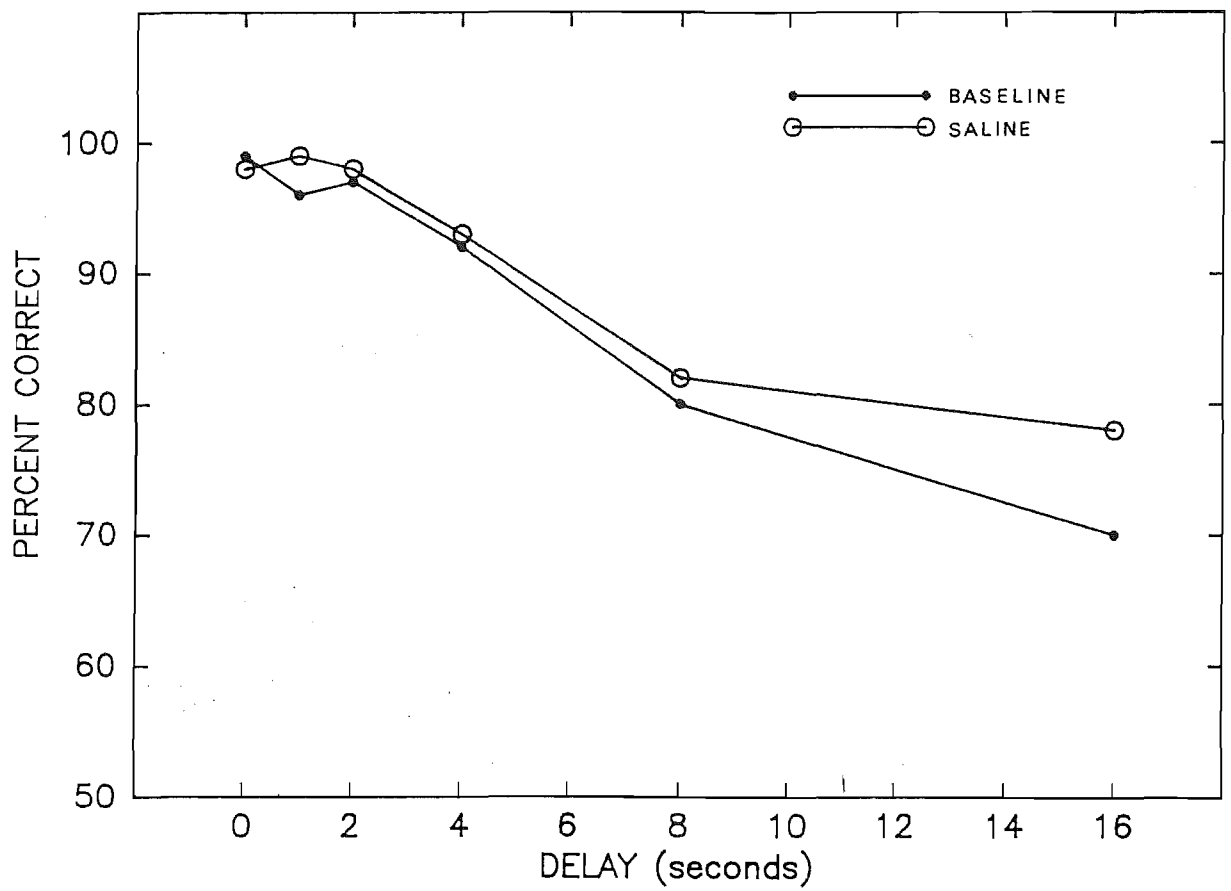


Figure 28. Percent correct for the baseline and saline conditions.

the discriminability data. Since bias was low, the percent correct and log d values were highly correlated ( $r = .95$ ). A ceiling effect was more apparent in these data than in the discriminability data, especially in the saline condition. The percent correct data were transformed using an arc sine transformation to normalize the data (Winer, 1962) and a two-way repeated measures analysis of variance was run (Lane, 1981). There was no significant effect due to the conditions factor,  $F(1,4) = 2.82$ ,  $p > .05$ ., but the delay factor was significant,  $F(1,6) = 24.15$ ,  $p < .01$ . There was no significant interaction.

#### The Effects of Haloperidol on Performance

Since each dose was only administered to one subject, the data from individual subjects are presented separately. The data from the six sessions where haloperidol was administered have been pooled for each subject.

Measures of psychomotor performance. All the subjects showed some response failure during the six sessions when haloperidol was administered. Details of response failure by each subject across those six sessions are presented in Table 24. Two of the subjects failed to complete any of the six sessions and this was reflected in their low overall percentage of completed trials.

A comparison of the average centre key latency and side key latency in the saline and drug conditions for each subject is presented in Table 25. For all the drug conditions there was an increase in the latency measure. To standardize comparisons across the subjects, the increase as a percentage of the saline condition latency was calculated. For the centre key latency measure the increase in the latency was orderly until the highest dose was reached. The pattern

Table 24

Details of Response Failure for Each Subject

Subject Number	Dose (mg/kg)	Number of Completed Sessions*	Percentage of Completed Trials
6	.06	0	16.8
10	.07	3	74.0
7	.09	4	79.9
9	.20	1	53.3
8	.30	0	13.8

\* The maximum number of sessions was 6.



Table 25

Changes in the Mean Centre Key Latency (CKL) and Side Key Latency (SKL) (sec) Across the Saline and Drug Conditions for Each Subject

	Dose			Percentage	
Subject	(mg/kg)	Saline	Drug	Increase	t
I. CKL					
6	.06	4.89	5.99	22.5	-6.83***
10	.07	2.38	2.96	24.0	-4.78***
7	.09	2.50	4.32	72.0	-9.33***
9	.20	2.03	4.61	127.0	-6.71***
8	.30	2.94	4.62	57.1	-5.93***
II. SKL					
6	.06	1.48	2.12	43.2	-4.37***
10	.07	1.94	2.46	26.8	-5.00***
7	.09	1.78	2.07	16.3	-2.62*
9	.20	1.20	2.23	85.8	-8.23***
8	.30	1.34	1.78	32.8	-2.83**

\*  $p < .050$

\*\*  $p < .025$

\*\*\*  $p < .010$

for the side key latency data was not so orderly and again the highest dose did not affect subject number 10 as much as lower doses affected the other subjects. To compare the latency measures across the saline and drug conditions, t-tests were carried out on the data for each subject. The values obtained and the corresponding significance levels are also shown in Table 25. All the differences were significant at the 1% level except for the difference between the side key latency measure for subject number 7, which reached significance at the 5% level, and for subject number 8 where the difference was significant at the 2.5% level.

Bias. The number of red and green comparison stimuli responses following red and green sample stimuli for each of the drug doses is presented in Table 26. Though the maximum number of trials possible at each delay was 120, response failure meant that this maximum was not attained by any of the subjects. Point estimates of bias were able to be calculated for most of the delay values. These values are presented in Table 27. Bias values were small ranging from  $-.24$  to  $+.50$  with a mean absolute value of  $0.14$ . There were approximately equal numbers of positive and negative bias values although subject number 9, who received the  $0.20$  mg/kg dose showed a consistent, but small, bias toward responding on the green comparison key.

Discriminability. Had all the possible 120 trials at each delay been completed there is likely to have been sufficient data to calculate discriminability values for each of the subjects. However, response failure by all the subjects meant the maximum number of trials completed by any one subject was 95. In addition, the total number of trials completed across the delay intervals differed and since the log d values depend on the total number of trials, a

Table 26

Number of Red and Green Comparison Key Responses  
Following Red and Green Sample Stimuli for  
Each Subject

Subject	Dose (mg/kg)	Delay	C. R. GG	F. A. GR	Miss RG	Hit RR
6	.06	0	11	0	1	8
		1	11	2	4	14
		2	13	2	2	10
		4	4	3	0	12
		8	6	5	2	12
		16	9	4	4	9
10	.07	0	47	1	0	48
		1	38	3	0	42
		2	39	5	2	42
		4	36	8	9	33
		8	30	13	12	32
		16	31	20	18	23
7	.09	0	50	0	3	43
		1	45	4	1	45
		2	37	13	4	48
		4	38	6	6	42
		8	34	14	10	37
		16	34	11	17	33
9	.20	0	30	4	4	31
		1	20	10	12	19
		2	24	8	10	22
		4	20	11	13	17
		8	22	12	14	15
		16	18	14	24	10
8	.30	0	7	1	0	11
		1	3	1	0	7
		2	6	3	5	11
		4	3	4	4	3
		8	6	6	3	5
		16	2	4	2	3

C. R. = Correct Rejection

F. A. = False Alarm

Table 27

Point Estimates of Log Response Bias Across the Drug  
Conditions for Each Delay Interval

Delay	Dose (mg/kg)				
	.06	.07	.09	.20	.30
0	-	-	-	0	-
1	.01	-	.30	-.05	-
2	0	.22	.31	-.07	.02
4	-	-.04	0	-.07	0
8	.50	.03	.09	-.12	.11
16	0	-.04	-.10	-.24	.24

comparison of the log d values across the delay conditions would have been meaningless. Therefore the percentage correct data were used to analyze the drug effects. Since bias was low, percent correct provided a relatively bias free measure of performance.

Percent correct. The average percent correct for each subject for the saline and drug conditions across all delay values and the percentage decrease caused by the drug is presented in Table 28. The percentage correct obtained in the saline and drug conditions for each subject were compared using a t-test. The values obtained and the significance levels are also shown in Table 28.

For subject number 6, who received the 0.06 mg/kg dose of haloperidol, the percent correct at each delay level for the saline and drug conditions is presented in Figure 29a and the regression lines for the curves are shown in Figure 29b. Apart from performance at the zero second delay interval, the drug had a consistent effect on performance at all delay values. This is shown in the regression lines for the two conditions which are approximately parallel. The overall percentage decrease caused by the drug was 14.2%, which was significant at the 1% level.

The percent correct data and the regression lines for the saline and 0.07 mg/kg drug condition (subject number 10), are shown in Figure 30. Performance at the shorter delays was impaired in the drug condition but at the 8 and 16 second delay intervals, matching performance was improved in the drug condition. There was no significant difference in overall performance between the two conditions as shown by the similarity in the regression lines and the small percentage decrease across the two conditions.

Subject number 7 received the .09 mg/kg dose and the percent correct data and the regression lines are shown in Figure 31. Except

Table 28

Changes in the Mean Percent Correct Across the Saline and Drug  
Conditions for Each Subject

Subject	Dose (mg/kg)	Percentage			
		Saline	Drug	Decrease	t
6	.06	95.0	81.0	14.2	3.16***
10	.07	86.5	84.8	2.0	0.17
7	.09	91.3	85.0	6.9	1.11
9	.20	93.3	61.2	34.4	4.17***
8	.30	91.0	69.3	23.8	2.51*

\*  $p < .050$

\*\*  $p < .025$

\*\*\*  $p < .010$

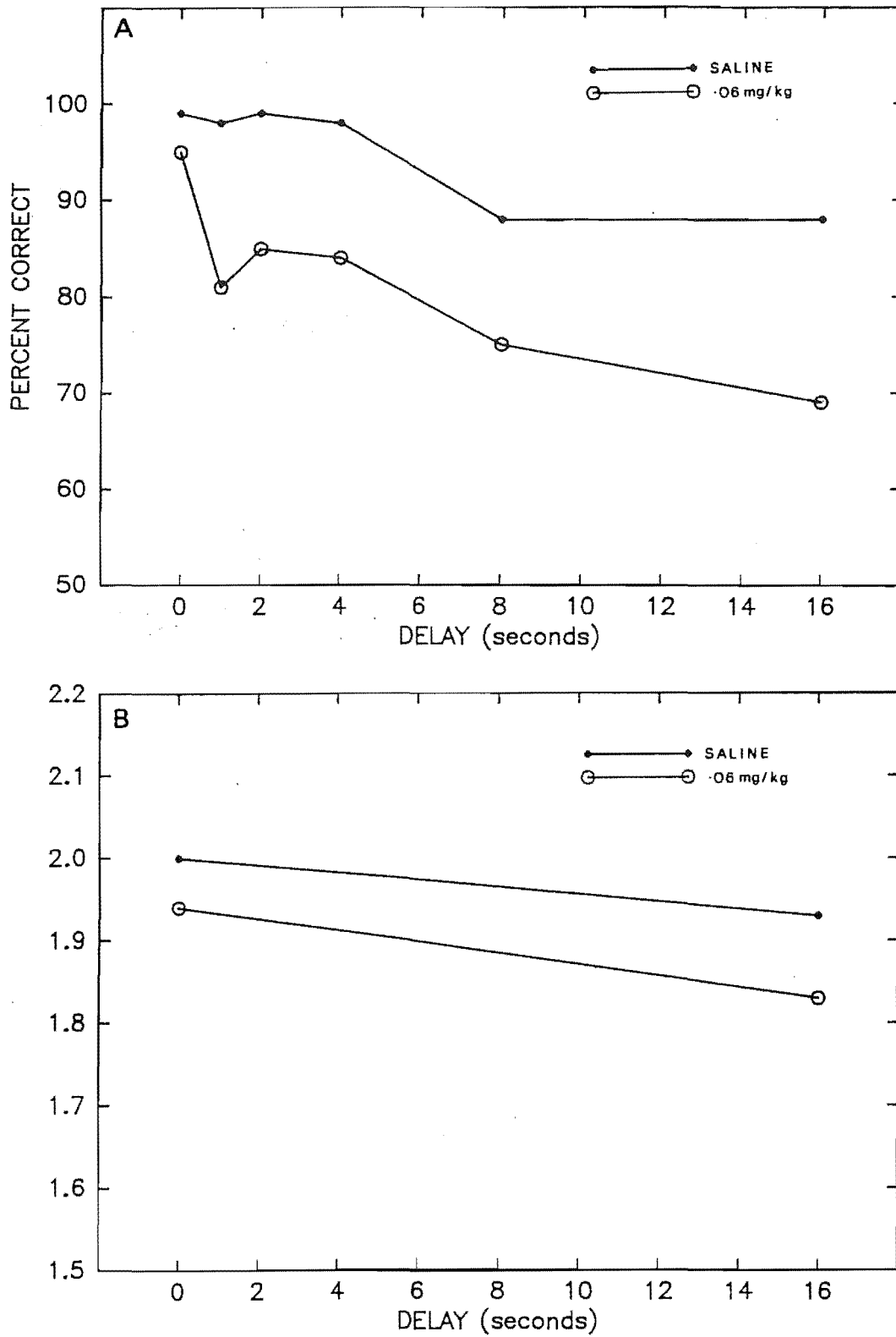


Figure 29. Data from subject number 6 for the saline and drug conditions: A. Percent correct B. Regression lines.

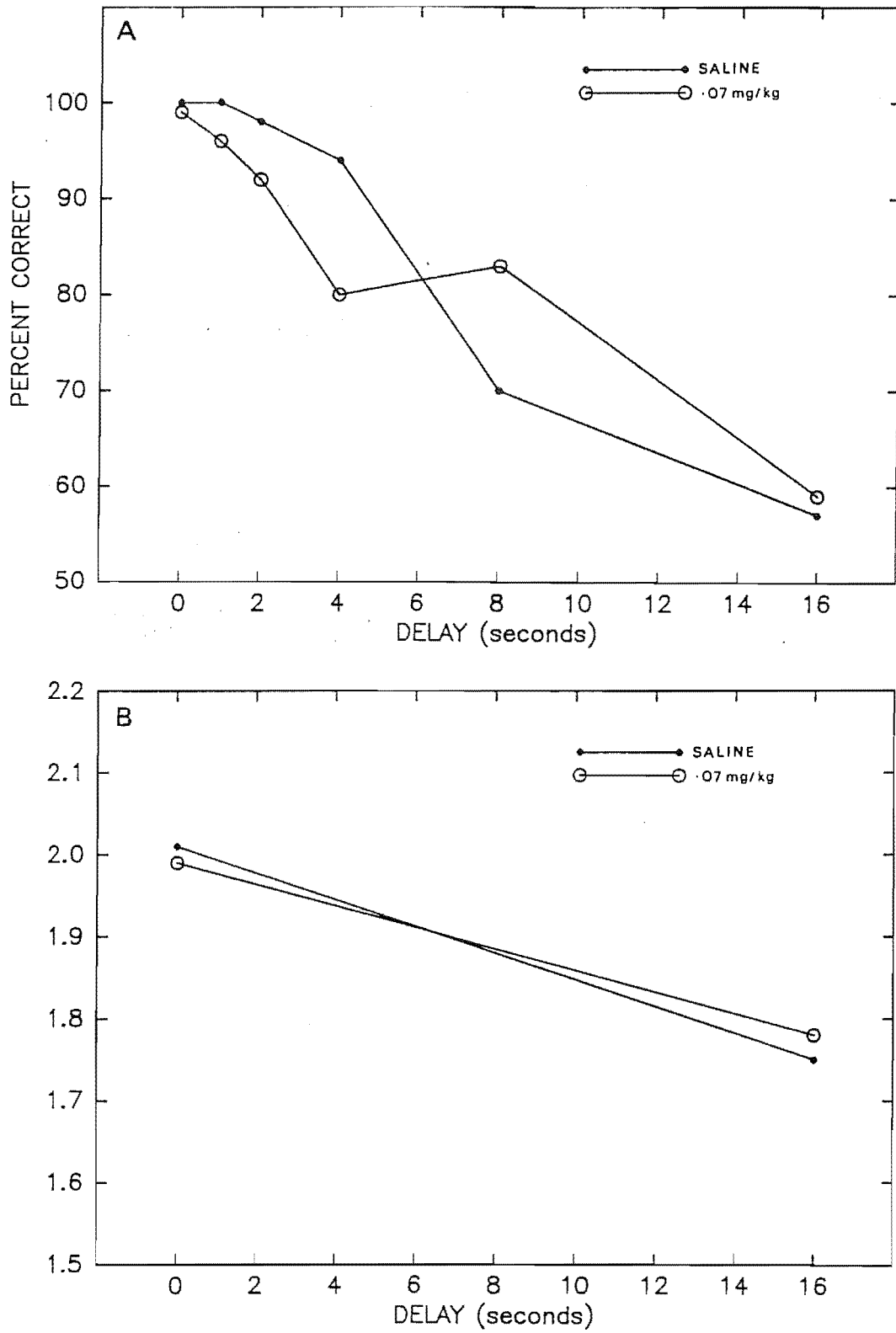


Figure 30. Data from subject number 10 for the saline and drug conditions: A. Percent correct B. Regression lines.



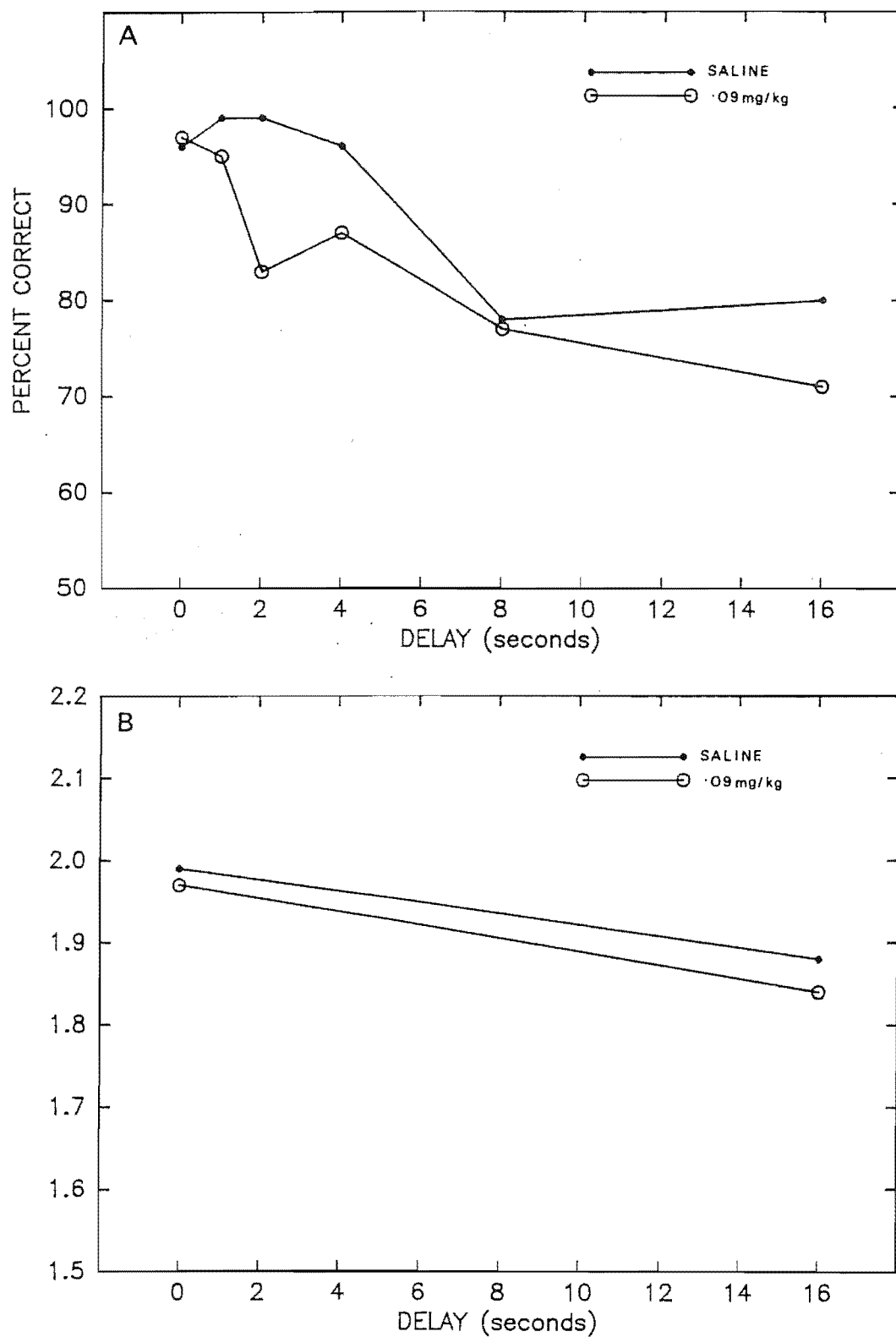


Figure 31. Data from subject number 7 for the saline and drug conditions: A. Percent correct B. Regression lines.

at the zero second delay, performance was less in the drug condition than in the saline condition. The overall percentage decrease caused by the drug was 6.9%, a non-significant decrease. The drug at this dose did not have a differential effect across the delay intervals as shown by the parallel regression lines.

Matching performance for subject number 9 across the saline and the .20 mg/kg drug condition is shown in Figure 32a and the regression lines in Figure 32b. The overall impairment was greater here than at any other dose, a percentage decrease of 34%, which was significant at the 1% level. Impairment in the drug condition across the delay intervals was erratic and twice fell below the chance level of 50%. Impairment across the delay values was similar as shown by the parallel regression lines in Figure 32b.

The data for the final subject (number 8), who received the .30 mg/kg dose is presented in Figure 33. In the drug condition percent correct remained above 90% until the 2 second delay interval when it rapidly decreased, falling below 50% at the 16 second delay interval. The overall percentage decrease was 23%, a difference significant at the 1% level. The divergence in the regression lines across the saline and drug conditions showed the drug had a greater effect at longer rather than shorter delay values.

### Discussion

The aim of this experiment was to use the behavioural model of signal detection to assess the effects of haloperidol on DMTS performance. A further aim was to compare the results obtained for haloperidol with those obtained in Experiment 1 for CPZ.

Most experiments in behavioural pharmacology involve the administration of a range of drug doses to a group of subjects and

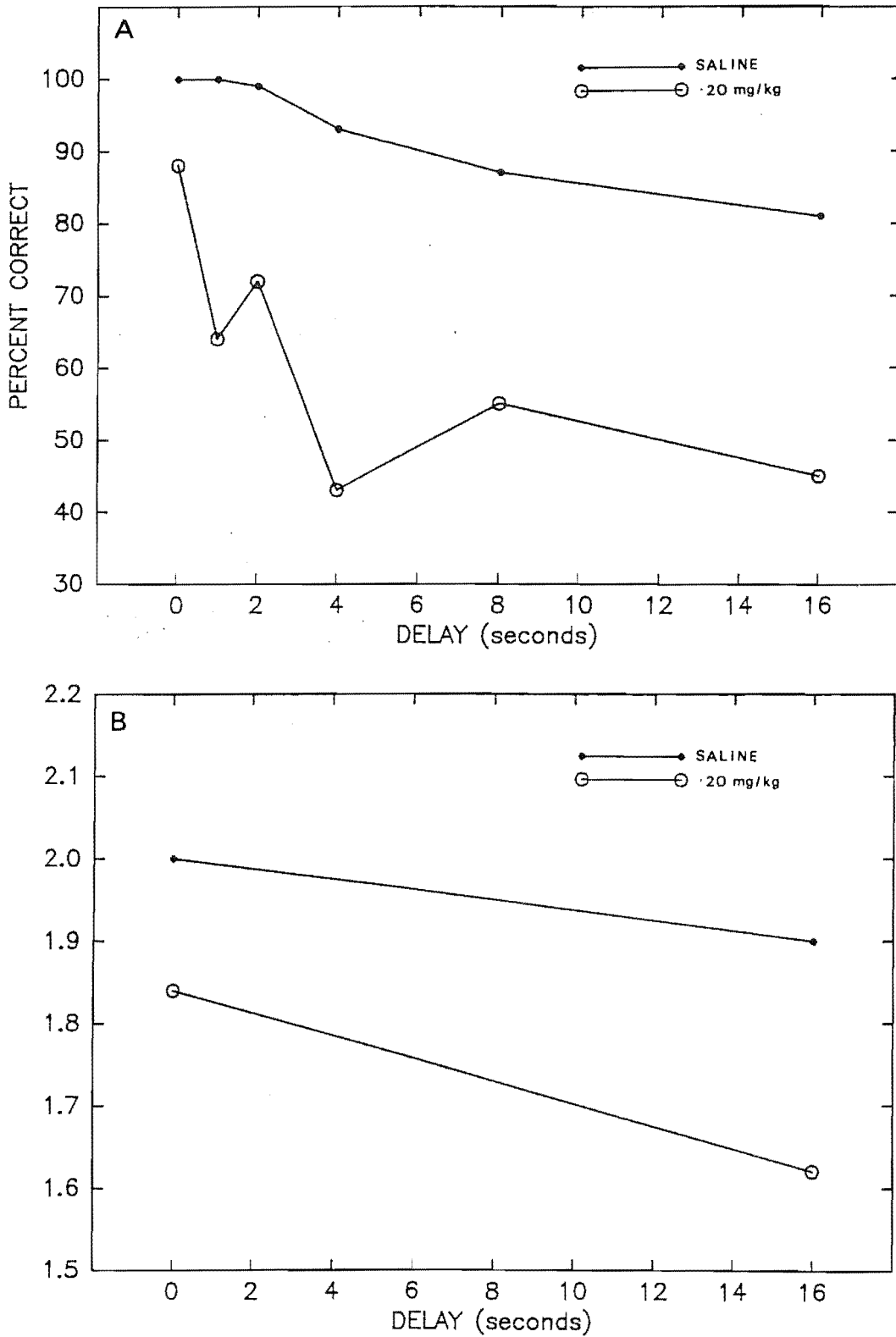


Figure 32. Data from subject number 9 for the saline and drug conditions: A. Percent correct B. Regression lines.

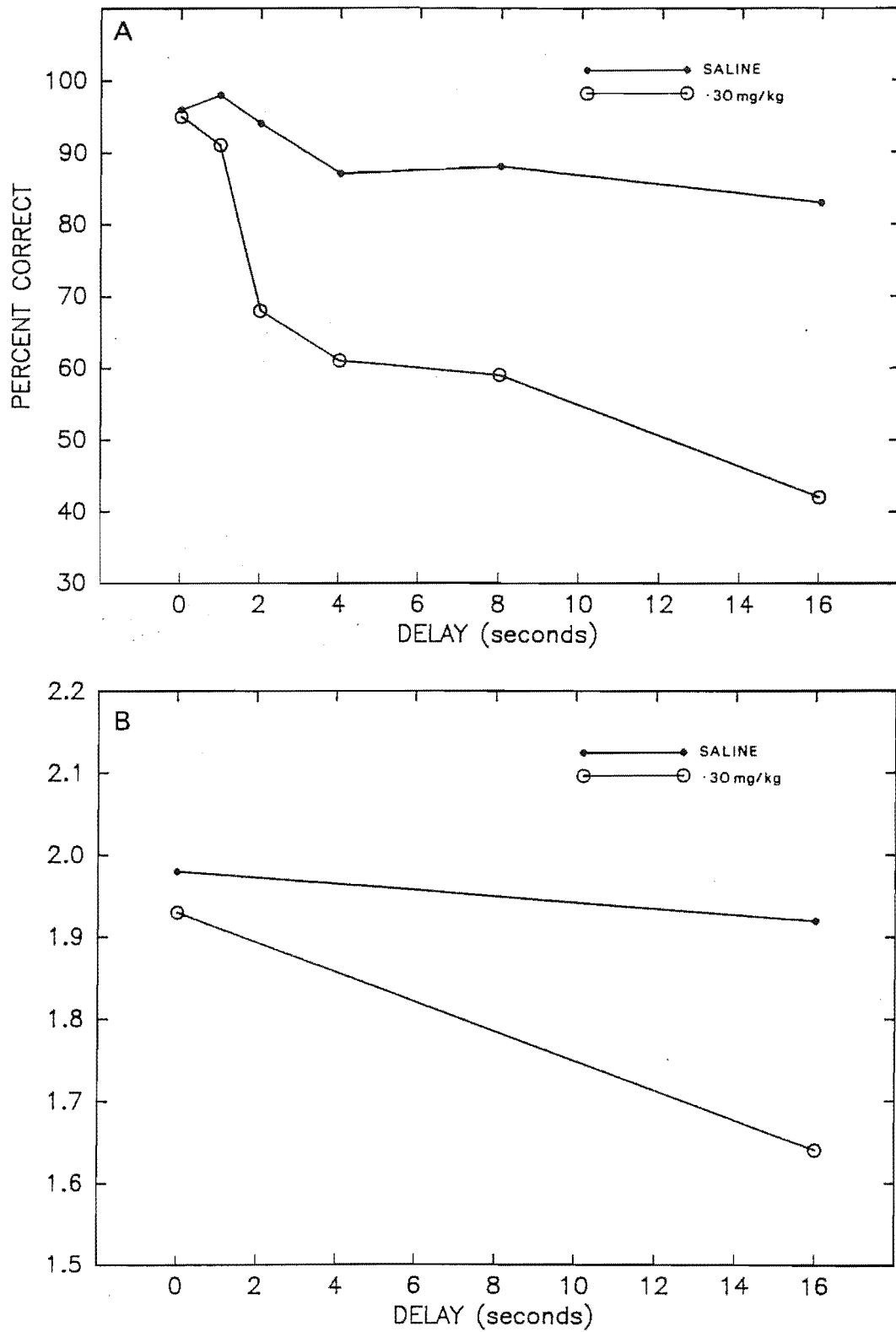


Figure 33. Data from subject number 8 for the saline and drug conditions: A. Percent correct B. Regression lines.

then a comparison between performance in the drug condition and that in a baseline condition. When group designs are used to evaluate the drugs, individual differences are lost when data are averaged across the subjects. Indeed, in Experiment 1 in this series, it was not until an analysis of data from the individual subjects was carried out that it was apparent that one subject appeared unaffected by any dose of CPZ. This raises the issue of individual susceptibility of subjects to various drugs. In Experiment 1, there were marked differences between subjects in not only their baseline level of performance but also the degree to which performance decremented in the drug condition.

In the present experiment it was obvious from the beginning of the first drug trial, when dose levels of 0.1, 0.25, and 0.5 mg/kg were being tested, that the dose levels the subjects could tolerate differed widely. While most of the subjects completed some trials at the two lower dose levels, only one subject completed all trials at the 0.5 mg/kg level. In addition, the same dose given to the same subject on different occasions had differing effects. Since little useful data were being obtained from the first drug trial, this was abandoned and a dose level was determined for each individual subject. In an attempt to standardize this dose level across subjects, a dose where each subject was reliably completing all 120 trials per session was chosen. Although this was a stringent criterion, it was necessary in order to gain sufficient data to apply the behavioural model of signal detection.

The dose levels determined for the subjects fell into two groups: the three doses below 0.1 mg/kg were within a range of .03 mg/kg and the other two were considerably higher, 0.2 and 0.3 mg/kg. This gave a range in terms of CPZ equivalence of 3 mg/kg and 15 mg/kg and meant the results could still be compared with those obtained in Experiment 1.

Since all the subjects worked under the same conditions in the baseline and vehicle control phases of the experiment, data from the six sessions in each condition were able to be combined across the subjects. The acid-buffered saline which was used as the vehicle control, caused an increase in the two latency measures but this was only significant for the side key latency. This significant increase was probably due to the effect of the saline injections on just one subject. The mean side key latency for subject number 7 showed a much greater increase in the saline phase compared to the baseline phase, than did any other subject.

Matching performance in the saline condition, where saline sessions were interspersed with "drug" sessions, was greater than in the baseline condition, although the increase was not significant. This result was also found in Experiment 1, and it may indicate as previously postulated that exposure to the drug had a beneficial effect on the subjects' ability to perform the matching task during "non-drug" sessions.

Any interpretation of the effects of haloperidol must be extremely tentative and although a range of doses were administered, each subject received only one dose level. Therefore drug effects have been confounded with intra-subject variables, thus limiting the conclusions that can be drawn concerning the drug effects. Despite the dose level for each subject in the second drug trial being that at which they completed all trials per session prior to the formal drug trial, all the subjects showed some response failure during the six drug sessions. This was particularly severe for two of the subjects who did not complete all the trials in any one of their six sessions. It is unlikely that this repeated response failure was due to the drug accumulating in the subjects as there were washout days between each drug injection. Performance had to return to baseline levels before

the next drug injection was given. Also there was no increasing trend in the degree of response failure across the sessions for any subject, which would be expected if the drug was accumulating.

An important finding of this study is that haloperidol, at doses that were approximately equal to the doses of CPZ used in Experiment 1, caused both response failure and a statistically significant increase in both the centre and side key latency measures. By comparison, CPZ caused response failure only at the highest dose that was administered (15 mg/kg) and caused no significant change in the latency measures for the doses 0.5-12.5 mg/kg.

One of the major problems when assessing drug effects on discrimination and memory is to separate drug effects on psychomotor variables from those effects on discrimination and memory processes. Discrete-trials procedures minimize this problem by requiring only one response per trial and therefore performance is evaluated in terms of response probability rather than response rate. This means the percentage correct is usually used as the measure of performance. While signal detection theory provides a method of identifying the locus of changes in performance, the indices derived from the behavioural model of signal detection are not entirely unaffected by drug effects on psychomotor variables.

In this experiment, the bias index from the behavioural model of signal detection remained relatively unaffected by the response failure caused by haloperidol. This index is determined more by the relative distribution of responses in the signal detection matrix than it is by the total number. Therefore the bias index can be calculated and compared when there are different total numbers of trials in each matrix. In this case, the controlled reinforcement rate procedure kept bias low with no consistent trends as a function of either the delay or the drug dose.

However, the discriminability index,  $\log d$ , is much more susceptible to drug effects on psychomotor performance.  $\log d$  values cannot be meaningfully compared unless each value is calculated from a matrix with the same total number of entries. The changes in  $\log d$  as a function of the total number of entries in the matrix become greater when the total number of entries becomes small, as was the case in this experiment.

Therefore in this study, matching performance had to be assessed using the percent correct measure which, since bias was low, provided a close estimate of discriminative performance. However, as seen in previous experiments percent correct data are more likely to show ceiling effects at short delay values than are the corresponding  $\log d$  values. For 2 of the dose levels, .07 and .06 mg/kg, haloperidol caused a significant decrease in the latency measures but had no significant effect on matching performance. At the two highest doses there was a significant decrease in percent correct. While it is possible that this may represent a dose/response relationship, and the significant decrease in matching performance at the .06 mg/kg dose level was due to the high susceptibility of subject number 6, no firm conclusions can be drawn. Across all the dose levels matching performance in the drug condition did not fall to chance levels even when response failure was greatest. The percentage decrease caused by haloperidol was generally greater than that caused by CPZ. Across all the CPZ doses the average decrease in performance from saline levels was 9.6% but the corresponding average decrease for haloperidol was 16.3%. Therefore in this series of experiments, despite equivalent doses being tested, haloperidol had a greater effect on matching performance than did CPZ.

The absence of discriminability,  $\log d$ , values means the models of the decay functions cannot be fitted to the data. Therefore there



is no way of quantifying the nature of the drug-induced changes in performance. However, some indication of the nature of these changes is given by the pattern of the regression lines for the saline and drug conditions. Generally for all dose levels except the .30 mg/kg condition, the regression lines were approximately parallel, with three of the four showing decreases in the initial level of the regression line for the drug condition. This showed that the drug was affecting only the initial discriminability and not the rate at which the discriminability decayed across the delay intervals. This finding is in agreement with the findings in Experiment 1 and extends the conclusions drawn by Heise and Milar (1984) to haloperidol, at least for these doses. For the .30 mg/kg dose level, there was a divergence in the regression lines suggesting the drug had a greater effect at longer delays. However, few trials were completed by the subject at this dose level and the result may therefore be unreliable. Conversely, the result may suggest that at higher doses haloperidol affects both the rate of decay and the initial discriminability.

The results obtained in this study are interesting when compared to previous research. In only one of the other studies reviewed did the authors comment on individual differences in the responses of their subjects to haloperidol. Poling et al. (1984) reported that haloperidol produced a dose-dependent decrease in the rate of response for two of their subjects, while inconsistently affecting the response rate of the third subject. No study reports the disparity in dose levels tolerated by individual subjects that were found in this study.

Unlike the results of this study, several experiments, using pigeons as subjects and similar procedures, have found no reduction in matching performance at similar and higher doses than those used in this study. Neilsen and Appel (1983) used doses of haloperidol up to 2.0 mg/kg, and found no decrease in percent correct despite non-

responding in some subjects. Poling et al. (1984) using a DMTS procedure and doses up to 0.5 mg/kg found no consistent impairment at any delay value. Finally, Woodward et al. (1986) found, using a titrating DMTS procedure, that a 0.5 mg/kg dose caused no significant decrease in percent correct.

Given that the Woodward et al. experiment was carried out in the same laboratory using four of the five subjects used in this experiment, the results are especially puzzling. In that study although haloperidol caused response failure, there were no significant changes in centre or side key latency measures. In the present study, lower doses were used than in the Woodward et al. experiment, yet there was a significant effect on both latency and performance variables for several subjects.

One possible reason for the differences in the findings between this and previous research is the mode of administration of haloperidol. In this experiment injections were given intraperitoneally (IP). In the studies by Nielsen and Appel (1983) and Poling et al. (1984) injections were given intramuscularly (IM). Drug distribution is more rapid when the drug is administered by the IP compared to the IM route. Peak plasma levels occur sooner with IP injections and the peak level is higher than when IM injections are given (Thompson & Schuster, 1968). In the studies by Nielsen and Appel (1983) and Poling et al. (1984) as well as the present study, the injections were given 15 minutes prior to the start of the experimental session and each session lasted approximately one hour. Therefore in the present study the plasma levels of the drug would have been higher, and this may account for the greater effects of the drug.

However, this does not explain the results of this study in comparison with that of Woodward et al. (1986) where the drug was

given IP, as in the present study. Although haloperidol is not known to be a neurotoxin, it is possible that the subjects sustained some permanent damage following the study where they were given the 0.5 mg/kg dose level. This may account for their greater susceptibility to the drug in this study.

The study described here needs replication to determine not only the effect of haloperidol, but also its effect in relation to other neuroleptic drugs. This is important given the possibility that haloperidol may achieve therapeutic behavioural changes at doses that do not impair discriminative or matching performance. Given the difference in results obtained between doses of CPZ and haloperidol which were supposedly equivalent, a comparison of these two drugs carried out using the same subjects would clarify the nature of the relative drug effects. It would be preferable to use drug-naive subjects to limit any confounding of drug effects with the subjects past history.

The results of this study illustrate an area where the behavioural model of signal detection must be applied cautiously in the analysis of drug effects. If the discriminability values being compared across conditions are not based on the same total number of trials, changes in the log d values may not be directly attributable to the independent variable. This is only a problem when the total number of trials is small and is not sufficient reason to abandon the use of such analytic techniques.

## CHAPTER SEVEN

### General Discussion

The experiments presented in this thesis were concerned with evaluating the behavioural model of signal detection as a method of assessing drug effects on memory. In Experiment 1, pigeons working on a DMTS procedure received five doses of CPZ. At doses that caused a significant decrease in matching performance, there was no change in the measures of psychomotor performance. An analysis of the decay functions showed that the decrease in matching performance was due to a change in the initial discriminability. The drug caused no changes in the rate at which discriminability declined as the delay interval increased. This result was also found in Experiment 2, where the sample stimulus response requirement was systematically decreased from FR5 to FR1. In Experiment 3, an increase in the sample stimulus requirement prior to drug administration raised the baseline level of responding. This increased the level of performance when the drug was given relative to performance levels in Experiment 1 when the same dose was given. Finally in Experiment 4, the effects of haloperidol on DMTS performance were assessed. The method of analysis derived from the behavioural model of signal detection could not be applied as there was insufficient data. However, it was found that at equivalent doses to those of CPZ administered in Experiment 1, haloperidol caused a much greater decrease in both matching and psychomotor performance. The decrease in matching was due to a decrease in initial discriminability and not due to changes in the rate of decay.

Behavioural pharmacologists have long been concerned with drug effects on discrimination and memory processes. Such research can help to determine the nature of memory functioning as well as have a role

to play in building animal models of the actions of drugs used clinically in humans.

There are two areas of weakness in the methodology currently used in the assessment of drug effects on discrimination and memory. The first is the continued use of percent correct as the measure of performance. Signal detection theory (SDT) has shown that this measure is influenced by both perceptual sensitivity and response bias. When a drug causes a decrease in percent correct, unless a SDT analysis is carried out, it cannot be determined whether the decrease was due to drug effects on sensitivity, bias or both.

The second area of concern is the research using delayed discrimination techniques which has attempted to isolate behavioural processes that are being affected by drugs. This has been done using an analysis of the relationship between control and drug condition delay interval by performance curves. When performance in the drug condition is less than in the control condition, and when the curves are essentially parallel, a drug effect on discrimination processes only is inferred. When the control and drug curves diverge, an effect on retention or memory is inferred. Until recently there has been no way of quantifying these changes in performance as a function of the delay interval.

Research within the experimental analysis of behaviour has provided a quantitative analysis of discrimination and memory performance that has the potential to overcome the problems encountered in previous drug research. The behavioural model of signal detection (Davison & Tustin, 1978), and the subsequent extension of the model to account for delayed discrimination performance (McCarthy & White, in press; White, 1985) provides a new way of assessing drug effects. The aim of this thesis was to determine if the methods of analysis derived from the behavioural model of signal detection could

be used to analyze the effects of two neuroleptic drugs, chlorpromazine and haloperidol. The experiments in this thesis have shown that the application of this novel method of analysis is indeed feasible, and for CPZ the method of analysis was used to develop and test a model of the drug's action.

#### Methodological Issues

The major requirement for fitting the behavioural model of signal detection is that the experimental data be able to be cast into the traditional signal detection matrix. The number of hits, misses, false alarms, and correct rejections are needed to determine the point estimates of discriminability and bias. Most discrete-trials procedures involve differential responses after certain stimuli and therefore can be analyzed using this method. It therefore has wide generality and could be easily applied to the procedures currently used in the assessment of discrimination and memory.

For this form of analysis to be applied successfully, the data in the control and drug conditions must fall within the range of 50-100% correct or between 0 and the maximum log d value. The task for the subjects must be neither too easy nor too difficult. If the task is too easy there will be a ceiling effect in the data, where performance at short delay values cannot improve above 100% correct. If the task is too difficult, performance will fall to chance levels at the longer delay values and a floor effect will distort the data. In extreme cases, such ceiling and floor effects may distort the parameters of the decay functions measuring changes in discriminability over the delay interval.

In the present experiments there were several instances of ceiling effects in the data. These were more evident in the percent correct data than in the discriminability data. For example, in the

composite saline condition in Experiment 1, the percent correct values for the 0, 1, and 2 second delay values were clustered in the range of 98-99% correct, but the corresponding log d values were spread across a range of 0.15. There were no floor effects in the data as performance did not fall below 50% correct (or a log d value of 0), except in Experiment 4 where the decay functions were not fitted. Given this absence of floor or ceiling effects, the decay functions when fitted to the discriminability data in these experiments, are unlikely to have produced any distortion in the estimated rate of decay (b) or the half-life (h) measure.

The DMTS procedure is an ideal task for assessing performance over various levels of stimulus control. There are a number of procedural variables that are known to affect performance in characteristic ways (see Chapter One), and these can be altered to "fine-tune" the subject's baseline performance to the desired levels. In the experiments reported in this thesis, the relatively easy discrimination (red vs green), the FR5 response requirement on the sample stimulus, the relatively long ITI (15 seconds) and the inclusion of many short interval delays (0, 1, 2 seconds) all served to keep performance high in the baseline condition, even at the longer delay intervals. Had high performance at the short delay values created an unwanted ceiling effect, various options were available to decrease overall performance. For example, decreasing the sample stimulus response requirement, decreasing the ITI, or removing some of the short delay trials.

One advantage of the percent correct measure for use in drug studies was that it allows results to be compared across studies. Since the value of the discriminability measure, log d, depends on the number of trials which are distributed in the signal detection matrix, and since this is likely to differ markedly between studies, this

would appear to limit comparison across studies when this index was used. However, this could be overcome by converting log d values into a proportion of the maximum log d value obtainable given the total number of trials distributed in the signal detection matrix. The maximum log d value is obtained when there is just one error in both the miss and false alarm cells of the matrix. The point estimate of the maximum log d value then becomes:

$$\log d(\max) = 0.5 \log (\text{no. of hits})(\text{no. of correct rejections}) \quad (16)$$

The obtained log d values could be expressed as a proportion of this value as a way of standardizing the comparison of log d values across conditions with different total numbers of trials. Note, however, that this procedure can only be used when there is no response failure by any of the subjects. When subjects are failing to complete all trials, the maximum absolute log d value is a function of subject performance, and is no longer an independent variable in the experiments. Had different subjects been used in the experiments assessing CPZ in this thesis, the use of the obtained log d versus maximum log d ratio would have allowed comparison of the results across these studies. The ratio could also have been used to compare the baseline performance of the two groups of subjects used in these experiments. The measure could also be used to compare results across non-drug studies where the discriminability measure log d was used to assess performance.

Throughout this series of experiments a controlled reinforcement rate procedure was used. This is in contrast to previous drug studies where the relative frequency of reinforcers was able to vary with the subjects behaviour. When these uncontrolled reinforcement rate procedures are used, behaviour changes from being under the control of stimuli, when discriminability is high, to being under the control of reinforcers at low discriminability levels. However, when the



reinforcement rate is controlled, changes in preference cannot alter the relative distribution of reinforcers for the two response alternatives, and consequently behaviour is always under the joint control of the discriminative stimuli and the reinforcers. In order to assess drug effects, it was necessary to minimize bias in the subjects responding to attain a bias-free measure of discriminability.

In these experiments, the controlled reinforcement rate procedure meant bias was virtually absent. As in Harnett et al. (1984) bias did not change as the delay interval increased. Further there were no changes in bias across either the drug conditions in Experiment 1, or the sample stimulus conditions in Experiment 2, i.e., no changes in bias with changes in discriminability.

However, the drug may still have an effect on bias that was not apparent in this study. The Davison and Tustin model distinguishes two sources of response bias. One is a constant bias arising from the requirements of the experiment or from the subject itself, and the other arises from different numbers of reinforcements for the two choice responses. This latter component of bias is known as sensitivity to reinforcement. To determine an estimate of sensitivity to reinforcement, the relative distribution of reinforcers between the two choice responses must be varied. For each stimulus, Equations 9 and 10 are fitted (see Chapter Three), and the slope of the best-fitting line is an estimate of the reinforcer sensitivity measure. Unpublished research at the University of Auckland has found that some drugs may alter this measure. Children with high blood levels of lead have greater bias in their discrimination performance than subjects with normal blood levels. The stimulant methylphenidate, has also been found to have an effect on the bias measure. In a study evaluating the effects of verapamil with adult schizophrenics, at one dose level, an effect on discriminability was found, but at another dose level, there

was an effect on bias. This latter result is particularly interesting, suggesting that the effects of certain on discriminability and bias may be dose-dependent (I.L. Beale, personal communication, December, 1986). The issue of whether drugs affect discriminability, bias, or both is interesting theoretically and has some practical implications which will be discussed shortly.

Another methodological issue concerns the quantity of data needed for the analysis. In Experiment 1, injecting each subject three times at each dose level and pooling the data across the five subjects meant there were 300 trials at each delay for each dose level. The analysis was able to be successfully performed on grouped data, but there was insufficient data for an analysis of the performance of individual subject's at each dose. To generate more data, more trials could be run in each session. However, if the length of the session gets too long, there may be time-correlated changes in the drugs' effect across a single session. Session time could be reduced by using a shorter inter-trial interval, but this would cause a decrement in performance. In addition if there were a large number of trials in a session, the subjects may become satiated and performance would cease. Thinner schedules of reinforcement could be used, but as performance decreases at higher dose levels, for example, a "leaner" schedule may not be sufficient to maintain behaviour. The number of delay values could be reduced to allow more trials at each delay value per session. However at least four or five values are needed to reliably determine the decay functions (White, 1985), and the inclusion of many short delays keeps the overall performance level high (White & Bunnell-McKenzie, 1985). Therefore repeated administration would appear to be the only suitable way of generating sufficient data for the analysis. Given that washout days are required between each drug injection, this means the generation of a dose-response curve using this method of analysis

can be very time-consuming. In Experiment 4, repeated administration of haloperidol was used to collect data from individual subjects. Allowing three days for washout between each injection, this drug trial took 30 days to complete.

Branch (1984) comments that a solution to this problem may be to use the procedure of cumulative dosing described by Wenger (1980). This procedure allows the determination of a dose-response curve in a single session, and could easily be adapted to collect data for this form of analysis. However, the procedure should be used with caution as Thompson, Moersbaecher, and Winsauer (1983) found that for phencyclidine and phenobarbital, there were quantitative differences in the dose-response curves resulting from cumulative and non-cumulative dosing. Nevertheless, the procedure holds promise as a method of generating suitable dose-response data both for this form of analysis, where large amounts of data are needed, and in other areas of behavioural pharmacology as well (Branch, 1984).

#### A Model of Drug Action

The behavioural model of delayed discrimination performance postulates two factors which determine performance at a given delay value, the initial discriminability and the rate of decay. It is not unreasonable to suppose that drugs might act differentially on these two components. Some drugs may only disrupt discrimination while others may have a selective effect on remembering. For certain drugs there may also be differential effects depending on the drug dose, for example, memory processes may be affected at lower doses than those that affect discrimination processes.

Heise and Milar (1984) in a review of drugs and stimulus control concluded that drugs in general do not affect memory or retention processes but only the processes involved in zero-delay discrimination

performance i. e., discrimination, encoding, and retrieval. This conclusion was supported by the analysis of the effects of both CPZ and haloperidol carried out in this thesis. In Experiment 1, there was clear evidence that increasing doses of CPZ caused a decrease in the initial discriminability with no change in either the rate of decay,  $b$ , or the half-life,  $h$ . In terms of Heise and Milner's analysis of the processes involved in delayed discrimination performance, the drugs' effects were confined to discrimination, encoding, and retrieval processes with no effects on memory or retention. The drugs lowered performance in a way that suggested the discrimination became more difficult. Since there were no differential effects on performance as a function of the delay value, the drug did not make it difficult to remember the discrimination once it was made.

A model of CPZ action limiting effects to initial discriminability was supported by the results of Experiment 2. This experiment used the procedural manipulation of altering the sample stimulus response requirement to change the difficulty of the discrimination task. The results obtained as the discrimination became more difficult, mimicked those when increasing doses of CPZ were administered. Further support for the model of CPZ action came from Experiment 3 where the discrimination was made easier by increasing the sample stimulus requirement. This raised the overall level of stimulus control and meant the absolute level of performance following drug administration was increased.

The results of Experiment 4, which analyzed the effect of haloperidol, also suggest that the drug's effects may be limited to the initial discriminability parameter. Although there were methodological problems with this experiment, the results for all conditions except the highest drug dose level showed the drug did not have any differential effects as the delay interval increased. At the

highest drug dose the divergence in the control and drug performance by delay interval curves may be an artifact due to the small number of trials completed by the subjects or it could represent a drug effect on memory and retention that is only apparent at higher doses.

In general the results of these experiments provide support for Heise and Milar's conclusion concerning drug action on delayed discrimination performance. Similar results have now been found for a variety of drugs: scopolamine (Glick & Jarvik, 1970; Heise et al., 1976), d-amphetamine (Glick & Jarvik, 1969), sodium amobarbital (Hulme et al., 1979; Sahgal et al., 1980a), ethanol (Mello, 1971; Sahgal & Iversen, 1978), chlordiazepoxide (Sahgal & Iversen, 1980) and for CPZ and haloperidol. These drugs represent many different chemical classes of drugs: stimulant, benzodiazepine, anticholinergic, barbiturate, alcohol and neuroleptic. Given that similar results have now been obtained across various species and using different experimental procedures, this strongly suggests that this is a general drug effect. A broad spectrum of drugs with various modes of action may share the common attribute of not impairing memory or retention processes. Therefore, drug effects after various delay intervals may depend on the duration of the delay interval only to the extent that the interval affects stimulus control (Heise & Milar, 1984).

Until recently there has not been the experimental methodology to accurately examine these drug effects and this has led to inaccurate conclusions being drawn concerning the nature of drug effects on memory processes. The behavioural model of signal detection will allow further research to be carried out to determine if an effect on initial discriminability, and not the rate at which discriminability declines, is a general phenomenon of drug action. The generality of the phenomenon needs to be systematically determined for various different drugs with both theoretical and clinical interest.

Generality also needs to be tested across a variety of procedures, e. g. , delayed response versus delayed comparison procedures, simple versus conditional discrimination procedures, and for various modes of stimuli (visual, auditory, and spatial).

The interaction of various procedural manipulations and drug effects also needs to be determined. Of particular interest would be drug effects on performance following either the opportunity for rehearsal of the sample stimulus or the intrusion of distractor stimuli in the delay interval. Using the directed forgetting procedure and CPZ, for example, it is possible that a forget cue will cause a greater decrement in performance compared with non-drug performance. However, the discriminability of the forget and remember cues may also be decreased so the effect on matching accuracy may be less than expected.

#### Clinical Implications

The model of CPZ action proposed in this thesis is at present limited to the actions of drugs on the functioning of pigeons. The validity of the model in terms of the action of CPZ on human functioning has yet to be determined. However, a similar procedure and method of analysis could be readily carried out using human subjects. Such a method of analysis has clinical implications on two levels. First, it can help to determine which drugs cause cognitive impairment and whether there are differences between these drugs in the relationship between therapeutic efficacy and cognitive impairment. Second, the analysis can help to isolate the locus of cognitive impairment which is essential in developing ways to overcome this side effect of drug administration.

Some tentative comments can be made regarding the clinical implications of the results reported in this thesis. The experiments

in this thesis provided interesting information on the relationship between the psychomotor and cognitive effects for CPZ and haloperidol. For CPZ, doses that caused no significant reduction in psychomotor performance caused a statistically significant decrease in matching performance. Therefore doses that were too low to have the desired behavioural effect were causing cognitive impairment. Given that in a clinical situation higher doses would have to be administered to achieve the required therapeutic effect, presumably the degree of cognitive impairment would be even greater.

In the case of haloperidol, doses that were therapeutically equivalent to CPZ, and equivalent in terms of ED50 values for escape and avoidance responding, caused much greater psychomotor impairment. While haloperidol also caused a significant decrease in matching performance across the range of dose levels tested, it is possible that at lower dose levels, significant psychomotor impairment may be achieved with no concurrent impairment in cognitive functioning. If this proves to be the case it would be preferable to use such a drug in clinical situations.

For various reasons, it may not be possible to avoid administering a drug that causes a degree of cognitive impairment. The issue then becomes how to minimize this drug-induced impairment. If the animal model of drug action developed in this thesis is validated with human subjects it should be possible to apply the results of Experiment 3 when developing strategies to minimize impairment. In the case of CPZ, since it is likely that the discrimination is in effect made more difficult by the drug then, as shown in Experiment 3, a procedural manipulation that makes the discrimination easier will decrease the amount of cognitive impairment. In practical terms when teaching mentally retarded people, for example, this would involve accentuating stimuli used in teaching and training situations so it is

easier to tell them apart, i.e., the subjects' discriminability will be higher. The results of Experiment 3 suggest that this would aid performance in delayed discrimination tasks more than an intervention that focussed on memory or retention processes.

An important related issue is the difference between drug effects on discrimination performance established prior to, or concurrent with drug administration. The experiments by Thompson (1973, 1974), using repeated acquisition of behaviour chains, showed that CPZ had a greater effect on performance in a learning situation relative to its effects on a task the subjects had previously acquired. That is, in clinical terms, material taught while the subject is taking the drug would be more difficult for the subject to learn. This provides another strong supporting argument for the implementation of extended drug holidays for people on long-term neuroleptic drug treatment. Such drug-free periods would provide an opportunity for the easier acquisition of new skills.

As previously mentioned, some drugs have been found to have an effect on sensitivity to differential reinforcement. Given the important part played by explicit reinforcement contingencies in many teaching and therapy programs, it is important to understand the relationship between reinforcement sensitivity and drugs. It has been suggested that catecholamine pathways may be critical to the mediation of reward in the brain. Further there is considerable evidence that drugs interfere with catecholamine function, particularly with dopamine release (Wise, 1978). Since antipsychotic drugs have a pronounced blocking effect on dopamine (Creese, Burt, & Snyder, 1976), they may also interfere with reinforcement (Aman, 1984). In a review of research examining combinations of pharmacotherapy and reinforcement procedures, Aman and Singh (1986) concluded that none of the studies using developmentally disabled people as subjects



indicated interference with reinforcement effects, at least at the doses assessed. However, one study using patients with long term psychiatric illness suggested that neuroleptics may hinder aspects of behaviour therapy (Paul, Tobias, & Holly, 1972). Further development of the animal model of drug action using the procedures and forms of analysis derived from the behavioural model of signal detection may assist in understanding the interaction between drugs and reinforcement. This is an important issue with direct implications for the success of teaching and therapy programs.

When extending the findings of this research to clinical situations a major limitation is that the drugs were tested following acute administration i.e., single doses after which the drug was allowed to washout before the next administration. In clinical situations, drugs are rarely given in this "one-off" manner. They are generally administered continuously over long periods of time, i.e., chronic administration. Repeated administration of a drug can lead to a loss of its initial effect, a diminution known as tolerance. The phenomenon is characterized by three features: it occurs in response to repeated drug administration, it is revealed as a loss of effect relative to initial impact, and it results in greater amounts of the drug being required to reinstate the initial effect (Carlton, 1983).

Chronic administration of and development of tolerance to neuroleptics has been studied in animals using the escape and avoidance responding paradigm. Irwin (1960) reported the rapid development of tolerance to CPZ effects in rats working on a shuttlebox avoidance procedure. An initial dose of 30 mg/kg caused a 90% incidence of avoidance response suppression and 50% escape response suppression. After 14 days chronic administration of CPZ, almost complete tolerance to the drug effects had developed with less than 20% avoidance suppression and virtually no escape suppression.

However, this may not be a general effect of all neuroleptics as tolerance development has not been found with some other neuroleptics using a discriminated avoidance procedure, e.g., fluphenazine (Carlton, 1983).

In humans tolerance develops to the sedative effects of CPZ and other phenothiazines. This takes place over a period of days or weeks and has been demonstrated by a variety of objective tests (Goodman Gilman et al., 1980). Other than this, phenothiazines do not produce tolerance or physical dependence in the true sense, although some muscular discomfort and insomnia may occur with abrupt discontinuation (J.H. White, 1977). Little is known about the changes in the cognitive side effects of antipsychotic medication as doses are repeatedly administered.

It is possible to study the effects of chronic administration of drugs on matching performance in pigeons. The effects of acute and chronic administration of various anticonvulsant drugs on the DMTS performance of pigeons has been studied (Picker, White, & Poling, 1985; Poling, Picker, Vande Polder, & Clark, 1986). The experimental design used in the study of chronic drug effects could be easily adapted to allow an analysis using the behavioural model of signal detection. This would mean drug effects following acute and chronic administration could be compared. It is important to incorporate information concerning tolerance development to the cognitive effects of drugs into models of drug action as this issue is of clinical concern. If a drug shows acute effects on cognitive performance, but this decreases with repeated administration, such a drug should be used in preference to a drug where there is no tolerance development to cognitive side effects.

An interesting phenomenon was observed in the studies in this thesis which may be related to this issue. Despite the fact that only

acute doses were administered in this study there appeared to be global effects that resulted in enhanced levels of performance each time baseline was re-assessed. Administration of CPZ in Experiment 1 and the lower sample stimulus response requirements in Experiment 2, in both cases resulted in an increase in the baseline levels of matching performance. This was also observed in Experiment 4 where performance in the saline condition, which was interspersed with haloperidol injections, was higher than in the baseline condition. It is possible that exposure to the difficult discriminations (either as a result of the drug administration or a changed response requirement) enhanced performance on the standard matching task, and this resulted in increased baseline performance following these conditions. If this is the case it suggests that tolerance was developing to the effects of the drug. This effect needs replication, and whether exposure to the more difficult discrimination is the reason for the enhanced baseline performance or whether this was due to improved performance over time, needs to be evaluated.

#### General Implications of the Findings

The results from the experiments in this thesis have implications not only in terms of models of drug action, but also for the field of behavioural pharmacology in general. The results also have implications for the model of memory that the method of analysis was based on, and also for the analysis of behavioural control in general.

As a discipline behavioural pharmacology has recently been criticized for having moved away from an analysis of the behavioural mechanisms of drug action (Branch, 1984), and as a result having few general principles and no general theory (Heise & Milar, 1984). With the demise of rate-dependency as a pervasive explanatory concept in behavioural pharmacology, research diverged into two relatively

independent lines of inquiry; the study of drugs as discriminative stimuli, and the development of receptor binding techniques which were subsequently influential in the study of drug self-administration (Branch, 1984). Branch also argues that much current research in behavioural pharmacology is directed at pharmacological rather than behavioural questions, and consequently risks being absorbed into the field of pharmacology in general.

For behavioural pharmacology to survive the emphasis in research must move back to a characterization of drug effects in terms of the effects on behavioural processes. Of necessity, the behavioural processes themselves must be understood. For this reason, "the future of behavioural pharmacology holds the promise to using developments, both methodological and theoretical, in the experimental analysis of behaviour" (Branch, 1984, p. 519). Branch (1984) gives two examples of conceptual views not yet utilized by behavioural pharmacologists, first the concept of response strength (Nevin, 1974) and second the rate equation from which one can extract a measure of reinforcer value (McDowell, Bass, & Kessel, 1983; McDowell & Kessel, 1979).

A third example might may well have been the behavioural model of signal detection and the subsequent development of a behavioural model of memory (Davison & Tustin, 1978; McCarthy & White, in press; White, 1985). The methodology and conceptual analysis provided by the model has the potential to provide new avenues of research for the discipline of behavioural pharmacology. The analysis is able to quantitatively describe the relationship between drug effects and underlying behavioural processes. With a simultaneous discrimination procedure the analysis is able to differentiate drug effects on perceptual sensitivity from effects on response bias. As demonstrated in this thesis, when delayed discrimination procedures are used, the analysis is able to distinguish drug effects on zero-delay performance

from drug effects at longer delay values. Therefore it is possible to determine whether drugs are affecting discrimination, encoding, and retrieval processes or memory and retention processes.

An issue requiring further research is the distinction between drug effects at no-delay and zero-delay which will allow drug effects on discrimination to be separated from effects on encoding and retrieval processes (Heise & Milar, 1984). While the form of analysis itself can do little to tease out these effects, methodological refinements offered by the model (eg, the controlled reinforcement rate procedure) should assist in differentiating drug effects on discrimination processes from encoding and retrieval processes. A related issue is the precise characterization of the memory processes affected by drugs. Heise and Milar (1984) comment that scopolamine predominantly affects sensitivity rather than bias, but it is not yet known whether this is due to a change in "stimulus sensitivity", "attention", or some other as yet unknown process. Future research is likely to benefit from use of the controlled reinforcement rate procedure that will ensure minimum bias in the subjects responding.

Therefore the form of analysis using the bias-free measure of discriminability,  $\log d$ , and an analysis of the decay functions, provides a means to develop models of drug action that characterize, in a quantitative manner, drug effects on behavioural processes. The method of analysis has an important role to play in the continued development of behavioural models of drug action. Analysis of the decay functions will allow drug effects on memory processes to be determined. Use of the controlled reinforcement rate procedure will provide bias-free measures of performance that will assist in the analysis of drug effects on no-delay and zero-delay processes. In addition this method of analysis provides behavioural pharmacology with a strong link with continuing theoretical research carried out

within the experimental analysis of behaviour.

Though the primary aim of this thesis was to provide an analysis of drug effects, the results also provide information relevant to the behavioural model of memory. One area of debate in the literature at present is whether the rate at which discriminability declines as the delay interval increases is a constant, or changes as a function of delay interval length. The negative exponential and the rectangular hyperbolic models describe these two patterns of decay. It was not intended that the data in this thesis would be suitable to evaluate the nature of the decay function. Since the equations were fitted to a small number of data points in the experiments described, the root mean square values (which provide a measure of how well the data fits the model) were all low and therefore cannot be used to evaluate the models. In terms of an analysis of drug action the issue may not be very important, given that the locus of drug effects does not appear to be memory or retention processes.

White (1985) has proposed the possible independence of the two components describing the forgetting functions in a delayed discrimination procedure. Only one variable has so far been found to influence both the initial discriminability and the rate of decay parameter,  $b$ . An experiment carried out by White (1985) and a reanalysis of data from Roberts (1972), both comparing the effects of altering the intertrial interval, found variation in the initial discriminability and the rate of decay parameter. However, other studies of the effect of intertrial interval were reanalyzed and did not show the same effect, i.e., only the  $\log d_0$  value was affected. White (1985) comments that "where there tended to be a relation between  $\log d_0$  and  $b$ , the overall level of discriminability tended to be low" (p. 32). The model assumes therefore that the initial discriminability,  $\log d_0$ , depends on the sample stimulus

characteristics, whereas the measure of rate of decay are affected by changes in the delay interval conditions.

The results of Experiments 1 and 4 clearly showed that for CPZ and haloperidol the changes were limited, in most cases to the initial discriminability. There were no consistent changes in the rate of decay,  $b$ , or half-life,  $h$ , measures as a function of drug dose. This result adds support to the notion that the two parameters of the decay function, i.e., the initial discriminability and the rate of decay, may be independent.

The application of this method of analysis has the potential to assist in the analysis of an another model of pigeon memory. Honig and Thompson (1982) have developed a theory of pigeon memory concerned with prospective and retrospective memory processes (see Chapter One). Briefly, when prospective coding is used the response decision is made at the time the stimuli are presented and this is remembered through the delay interval. This can only occur when all the information needed to determine the response is provided by the initial stimulus, as in a delayed simple discrimination. Retrospective coding occurs during delayed conditional discrimination procedures when the information presented by the sample stimulus is insufficient to determine the response. This information about the sample must be retained during the delay interval and combined with post-delay stimuli to determine the appropriate response.

It has been suggested that retrospection may be more difficult than prospection if the latter requires less information to be retained (Cohen, Galgan, & Fuerst, 1986). Indeed it has been found that increasing the interval between the sample and test stimuli decreases performance more dramatically in delayed conditional discrimination than in simple discrimination in pigeons (Honig & Wasserman, 1981; Smith, 1967). Differences between the two memory

processes could be quantitatively analyzed using the method derived from the behavioural model of signal detection. This could be achieved by comparing performance in a procedure where the subjects are likely to use prospective coding, i.e., a delayed simple discrimination, with performance in a procedure where retrospective coding occurs, i.e., a delayed conditional discrimination. With the nature of the stimuli and the length of the delay interval constant across the procedures, the nature of the differences in overall performance could be determined, i.e., whether they were due to changes in the initial discriminability or the rate at which the information decayed across the delay interval.

There has been extensive analyses of the nature of prospective memory function, e.g., the research on response intentions, differential outcome expectancies, and anticipations of trial outcomes (Honig & Dodd, 1986). It is believed that subjects learn to anticipate features of the procedures within trials, features that are not differentially associated with the initial stimulus. "We also need to know about the process by which anticipations of trial characteristics modulate performance, whether they affect the processing or 'encoding' of the initial stimulus or the rate of forgetting" (Honig & Dodd, 1986, p. 96). By manipulating the subjects ability to anticipate trial characteristics, and assessing the nature of the resulting decay functions using the method of analysis derived from the behavioural model of signal detection, it is likely that this issue could be resolved.

Drug effects on retrospective and prospective coding processes may differ. Presumably the degree of sample stimulus control is greater in prospective than in retrospective processing. Since in general terms drug effects depend on the degree of stimulus control, these effects would be seen first (at the lowest dose) where



retrospective coding was occurring. Heise and Milar (1984) report some discrepancies in the results of drug studies depending on whether a delayed response or a delayed comparison procedure was used. In a delayed response procedure prospective coding of information is likely to be occurring and in a delayed comparison procedure retrospective memory processes are probably used. This is an interesting finding and suggests there may be an interaction between drugs and the nature of the discrimination or memory task. The method of analysis described in this thesis would appear to have a valuable role to play in the quantification of these effects.

One final issue requires comment. The results of this thesis show that drug effects appear to be confined to discriminability. In drug experiments "memorability" of stimuli is dependent on the degree to which the initial discrimination of the stimuli is decreased by drug action. Specific drug effects on memory or retention processes appear not to occur. This places discriminability in the role of prime determinant of discrimination performance regardless of the presence of delay intervals in the procedures.

The role of discriminability has been widely investigated within stimulus control research. The behavioural model of signal detection provides the most extensive and complete analysis of the role of discriminability in both discrete trial psychophysical experiments and free-operant multiple concurrent schedule discrimination tasks. In addition the model has clarified the relationship between discriminability and differential reinforcement in detection experiments.

Much of the work within schedule control research has been concerned with the way subjects allocate their behaviour when faced with two schedules which allocate reinforcers in different patterns. The generalized matching law (Baum, 1974) is able to account well for

performance on such concurrent schedules. Recently reinforcement itself has been dealt with as a detection process. Davison and Jenkins (1985) provide a reinterpretation of the sensitivity to reinforcement parameter in the generalized matching law as contingency discriminability. They suggest that in a concurrent schedule "the subject's task is to decide, after each reinforcer delivery, which of two response classes produced the reinforcer. Thus in detection-theory terms, the stimuli to be detected are the delivery of reinforcers for one response (R1) and the delivery of those for the other response (R2)" (Davison & Jenkins, 1985, p. 78). Therefore the allocation of reinforcers depends on the subject's ability to discriminate the current environmental events. Combined with the theoretical accounts of bias and stimulus effects, the theory now provides a powerful account of the role of detection of environmental events and how they control behaviour.

It is possible to speculate on the basis of the Davison and Jenkins (1985) analysis and the results of the experiments reported in this thesis, that discriminability has a pivotal role in the interactions between organisms and their environment. Its role in the antecedent control of behaviour is well established and the Davison and Jenkins' analysis postulates a discriminability component in the law of effect. The experiments in this thesis show that an effect on discriminability is solely responsible for the effects of CPZ and probably also for haloperidol. Should this effect be replicated using other drugs, it would provide further evidence of the importance of discriminability.

In summary, continued research using the behavioural model of signal detection, and its extension to account for delayed discrimination performance, will be important in two ways. First it will provide quantitative analyses of drug effects on behavioural

processes and will greatly assist the development of models of drug action. Second, such drug research has the potential to assist in the analysis of the complex behavioural processes involved in discrimination and delayed discrimination performance, as well as in the analysis of behaviour in general.

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